APPENDIX B

Sensitivity of Cooper Statistics to the Number and Choice of Chemicals Used in Validation Study

Endocrine Disruptor Screening Program

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INTRODUCTION AND BACKGROUND

The predictive capacity of an assay being validated is frequently expressed by comparing the results obtained with the assay being validated on a sample of chemicals with the results of reference values on the same chemicals where the reference assay results are taken as the true values. The reference data may be generated from an original test that the new test is replacing, it may be in vivo data, or it can be other data that is considered to be authoritative and an appropriate basis for the evaluation of the predictive capacity of the assay being validated.

Objectives

This report addresses the precision of the estimates of the Cooper statistics as a function of the number and choice of chemicals sampled from the underlying population of chemicals. It illustrates the change in precision of the estimates as the sample size increases and provides an indication of the numbers of chemicals needed to estimate the Cooper statistics reasonably precisely. In particular it addresses the question of whether meaningful estimates of the parameters typically used in these comparisons can be obtained based on relatively small numbers of reference chemicals, such as one to two dozen. One important variable that was assumed for these comparisons was the proportion of the universe of chemicals that are endocrine disruptors (the probability of a true positive or positive prevalence, denoted by τ). Three scenarios were investigated: with $\tau = 0.01$, 0.05, and 0.1)

Cooper Statistics

In the case when the assay being evaluated and reference values are expressed simply as positive or negative, the outcome of the test assay validation study can be displayed in a 2×2 matrix whose rows represent the reference results and whose columns represent the test assay results. Such a 2×2 matrix is shown below for test results for the complete applicability domain or portion of the universe of chemicals to which the test applies (Designated as the population). N= the number of chemicals in the population. N_+ represents the number of positives and N_-, the number of negatives. The entries A, B, C, and D represent numbers of chemicals and total to N.
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Population Frequencies		**Test Method Values**		
		Positive	Negative	Total
Reference Values	Positive	A	B	$N_+ \equiv A+B$
	Negative	C	D	$N_- \equiv C+D$
	Total	A+C	B+D	$N \equiv A+B+C+D$

The 2×2 matrices displaying the results of test assay validation studies are often summarized by various characteristics of the test assay and the population of chemicals. In medical and toxicological applications they are sometimes referred to as "Cooper statistics" (Cooper et. al, 1979).

Cooper et al. summarize the performance of an assay (+ or -) in the particular population under consideration by the following population based characteristics:

(1) Sensitivity ≡ Prob [Assay Predicts Positive| True Positive]= A/(A+B) ≡ A/N_+ ≡ SNS
(2) Specificity ≡ Prob [Assay Predicts Negative| True Negative] = D/(C+D) ≡ D/N_- ≡ SPC
(3) Positive Predictivity ≡ Prob [True Positive|Assay Predicts Positive] = A/(A+C) ≡ PP
(4) Negative Predictivity ≡ Prob [True Negative|Assay Predicts Negative] = D/(B+D) ≡ NP
(5) Concordance ≡ Prob [Truth and Test Assay Prediction Agree] = (A+D)/(A+B+C+D) ≡ (A+D)/N

In addition, an important population characteristic that can affect the values of the summary characteristics is the probability that a randomly chosen chemical is positive. Namely

(6) Probability of True Positive ≡ Prob [True Positive] = (A+B)/(A+B+C+D) ≡ (A+B)/N ≡ τ

Sensitivity and specificity are characteristics of the test on this particular population of chemicals. Probability of true positive is a characteristic of the population of chemicals.

Reference Chemicals (a sample of the applicability domain)

Since the values in the above table are population values, they are usually unknown and need to be estimated from a sample. If a simple random sample of n chemicals is drawn from the population of N chemicals the sensitivity, specificity, positive predictivity, negative predictivity, concordance, and probability of true positive can each be estimated by substituting the sample frequencies a, b, c, d for the population frequencies in the expressions shown above. Depending upon the appropriate marginal totals, statistical inferences about these parameters can be based on the binomial distribution or the multinomial distribution.

Let a, b, c, d represent corresponding frequencies from a sample of n chemicals from the population of N chemicals (e.g. N = 9,000; n=200). The sample results can be displayed in a corresponding 2×2 matrix.

Sample Frequencies		Test Method Values		
		Positive	Negative	Total
Reference Values	Positive	a	b	$n_+ \equiv a+b$
	Negative	c	d	$n_- \equiv c+d$
	Total	$t_+ \equiv a+c$	$t_- \equiv b+d$	$n \equiv a+b+c+d$

The sample of n chemicals can be drawn from the population of N chemicals in various ways.

- A simple random sample of chemicals can be drawn from the population. In this case all the marginal totals are random.
- The frequencies n_+ and n_- can be fixed (e.g. $n_+ = 100$, $n_- = 100$) and random samples of size n_+ and n_- drawn from the subpopulations of true positive chemicals and true negative chemicals respectively.
- The frequencies t_+ and t_- can be fixed (e.g. $t_+ = 80$, $t_- = 120$) and random samples of size t_+ and t_- drawn from the subpopulations of test positive chemicals and test negative chemicals respectively.

These sample types can be mixed and matched. Each type of sample permits direct estimation of different population characteristics.

A simple random sample from the population

If stratified random samples of n_+ chemicals from the population of N_+ true positive chemicals and n_- chemicals from the population of N_- true negative chemicals are drawn, sensitivity and specificity can each be estimated by substituting the sample frequencies a, b, c, d for the population frequencies in the expressions shown above. Statistical inferences about these parameters can be based on the binomial distribution. However since the proportions n_+/n, n_-/n of true positive and true negative chemicals in the sample are specified by the sampling design and are not related to the proportions N_+/N, N_-/N of true positive and true negative chemicals in the population, positive predictivity, negative predictivity, concordance, and probability of true positive cannot be estimated by simply substituting sample frequencies for population frequencies. However, if the probability of a true positive $\equiv \tau$ can be estimated from outside the sample, positive predictivity and negative predictivity can be expressed in terms of sensitivity, specificity, and τ by Bayes' rule. Namely

(7) Positive Predictivity $\equiv$ PP = $SNS \times \tau / [SNS \times \tau + (1-SPC) \times (1-\tau)]$

(8) Negative Predictivity $\equiv$ NP =

$$SPC\times(1-\tau)/[SPC\times(1-\tau) + (1-SNS)\times\tau] \equiv 1 - \{(1-SNS)\times\tau/[SPC\times(1-\tau) + (1-SNS)\times\tau]\}$$

Fixed frequencies of test results (t_+ and t_-)

Similar considerations apply under the third sampling scheme, but with the roles of (sensitivity, specificity) and (positive predictivity, negative predictivity) reversed. Namely if the population probability Prob [Assay Predicts Positive] ≡ ρ can be estimated from outside the sample (e.g. by running the test assay on all or on a sample of the chemicals in the population), sensitivity and specificity can be expressed in terms of positive predictivity, negative predictivity, and ρ.

The implications of these relations are that all the Cooper statistics can be estimated without having to perform the test assay on a strictly random sample of chemicals. A random sample of chemicals from the population, stratified random samples based on the results of the reference method, or stratified random samples based on the results of the test assay can be drawn. These sampling strategies can also be mixed and matched and the results combined as appropriate.

Methods

The results are based on a Monte Carlo study that was carried out to estimate the sensitivity of the Cooper statistics estimates as the number of reference chemicals sampled varies and as the allocation of the sampled chemicals among true positives and true negatives varies. It is assumed that the reference status for each of the sampled chemicals is known, based on literature reports from well established assays that were carried out on them and/or on the agreement of test results among multiple assays and/or multiple laboratories.

In the Monte Carlo study the number of true positive chemicals sampled, n_+, and the number of true negative chemicals sampled, n_-, are assumed to be fixed. Thus sensitivity and specificity can be estimated based on substituting sample values in expressions (1) and (2). However positive predictivity and negative predictivity must be estimated based on substituting the estimates of sensitivity and specificity into expressions (7) and (8). The value of τ is assumed to be known.

A sensitivity analysis was carried out to determine the effects of variation in n_+, n_-, and τ on the inference precision of the Cooper statistics estimates. The population values of SNS and SPC were fixed and the values of n_+, n_-, and τ were varied over specified ranges. Given the assumed population values of SNS, SPC, and τ the population values of PP and NP are uniquely determined from relations (7) and (8).

For each combination of (SNS, SPC, τ, n_+, n_-) 1,000 simulated frequencies, a and d, were generated based on 1,000 independent binomial random variates with distributions binomial(n_+,SNS) and binomial(n_-,SPC) respectively. This sampling scheme assumes that the sampled chemicals are independent. The question of dependence among the results of the test assay among different chemicals will be discussed later in the report.

For each of the 1,000 simulated frequencies, a and d, sensitivity and specificity were estimated as

$$sns = a/n_+, \quad spc=d/n_-$$

Estimates of positive and negative predictivity were obtained by substituting sns and spc into expressions (7) and (8) above, respectively. Across the 1,000 simulations this generated empirical probability distributions for sensitivity, specificity, positive predictivity, and negative predictivity. The 95% confidence intervals for the Cooper statistics were taken to be the 2.5^{th} and the 97.5^{th} percentiles of the empirical probability distributions.

Two combinations of the population values SNS and SPC were assumed:

$$SNS = 0.90, \quad SPC=0.90$$

SNS = 0.90, SPC = 0.50

The first combination assumes that the population sensitivity and the population specificity of the test assay are reasonably high. The second combination assumes that the population sensitivity of the test assay is reasonably high but that the assay results in a sizable number of false positives. For each combination of SNS and SPC the assumed value of τ is assumed to be 0.10, 0.05, or 0.01. This results in six combinations of population characteristics.

For each combination of population parameters SNS, SPC, and τ the assumed numbers of true positive and true negative chemicals sampled was set at $n_+ = 10, 25, 50, 100$ and $n_- = 10, 25, 50, 100$. The Monte Carlo results for each parameter combination are displayed in an individual table. In each table the population values of sensitivity, specificity, positive predictivity, and negative predictivity are shown at the top. For each of the 16 combinations of n_+ and n_- and each of the Cooper statistics the Monte Carlo sample based mean, standard deviation, and lower and upper 95% confidence bounds are displayed.

Corresponding to each of the six tables three figures are included. Each figure displays the Monte Carlo based confidence intervals on each of the four Cooper statistics as a function of sample size. In the first figure it is assumed that equal numbers of positive and negative chemicals were sampled: $n_+ = n_- = 10, 25, 50, 100$. In the second figure it is assumed that n_- was held fixed at 25 and $n_+ = 10, 25, 50, 100$. The third figure it is assumed that n_+ was held fixed at 25 and $n_- = 10, 25, 50, 100$.

In each of these tables and figures it is assumed that the chemicals were sampled independently from subpopulations of true positive and true negative chemicals. Following the results section it is discussed how the sensitivity might be anticipated to be modified if the test assay results are assumed to be correlated among the test chemicals.

Results

Tables 1 to 3 display 95% confidence intervals associated with SNS=0.9, SPC=0.9, and τ = 0.01, 0.05, 0.1. These confidence intervals are also displayed graphically in Figures 1-a to 3-c. In these figures the horizontal reference lines (dotted) correspond to the population values of the Cooper statistics.

For given population values of SNS and SPC and with the stratified sampling design assumed in this study, the precision of the sensitivity and specificity estimates depends only on the sample sizes and not on τ. The precision of the sensitivity estimate depends on n_+ and the precision of the specificity estimate depends on n_-. When n_+ and n_- are 10 or 25 the confidence intervals on SNS and SPC are very wide. Thus inferences about these parameters are imprecise. The improvement in precision gained by increasing sample size from 25 to 50 is not much better than that obtained by increasing sample size from 10 to 25. Very little improvement in precision

is gained by increasing sample size from 50 to 100.

Positive predictivity and negative predictivity depend on τ and well as on SNS and SPC. Positive predictivity is relatively low. For SNS and SPC equal to 0.90 it decreases with τ, from PP=0.5 when τ=0.1 to PP=0.08 when τ=0.01. This means that if the test assay infers that the chemical is positive, there is considerable probability that it in fact is negative. This probability of error increases as τ decreases. Precision of inference about PP is sensitive to n_- (Figures 1, 2, 3-c) but not to n_+ (Figures 1, 2, 3-b). For n_- = 10 or 25 the confidence intervals on PP are so wide as to be uninformative. Not until n_- = 100 are the confidence intervals sufficiently narrow to be able to infer that the positive predictivity of the test assay is low.

Negative predictivity is very high. It increases from NP=0.99 when τ=0.1 to NP=0.999 when τ=0.01. This means that if the test assay infers that the chemical is negative, there is very considerable probability that it in fact is negative. Precision of inference about NP is sensitive to n_+ (Figures 1, 2, 3-b) but not to n_- (Figures 1, 2, 3-c). NP can be determined to be high even when n_+ = 10 or 25.

Tables 4 to 6 display 95% confidence intervals associated with SNS=0.9, SPC=0.5, and τ = 0.01, 0.05, 0.1. These confidence intervals are also displayed graphically in Figures 4-a to 6-c. In these figures the horizontal reference lines (dotted) correspond to the population values of the Cooper statistics.

Since the specificity of the test is assumed to be lower than in the previous discussion, more chemicals would be anticipated to be misclassified. This implies that with SPC=0.5 both the positive predictivity and the negative predictivity are lower than when SPC=0.9. Negative predictivity is still very high, going from NP=0.98 when τ=0.1 to NP=0.998 when τ=0.01. Positive predictivity is very low, going from PP=0.17 when τ=0.1 to PP=0.018 when τ=0.01. This again implies that if the test assay infers that the chemical is negative there is a very high probability that it in fact is negative. However if the test assay infers that the chemical is positive, the probability is still high that it in fact is negative.

When n_-=10 or n_-=25 the expected confidence interval on SPC is too wide to permit precise inferences to be made. The inference precision is a little better when n_- exceeds 50 but there is little improvement in precision between n_-=50 and n_-=100. It is necessary to sample at least n_-=50 true negative chemicals or better n_-=100 true negative chemicals in order to make reasonably precise inferences about SPC.

Inference precision about positive predictivity is primarily sensitive to n_- and less sensitive to n_+. Positive predictivity is low, and this can be inferred even with n_-=10 true negative chemicals. However to precisely estimate positive predictivity requires at least n_-=50 true negative chemicals or better yet n_-=100 true negative chemicals.

Inference precision about negative predictivity is good even when n_- and n_+ are 10 or 25.

It can be inferred that negative predictivity is high. Inference precision improves some between n_-=10 and n_-=25, but little beyond that. For example when τ=0.1 and $n_- = n_+$=10, the expected lower confidence bound on positive predictivity is 0.90 (population value=0.98). If $n_- = n_+$ increase to 25, the expected lower confidence bound increases to 0.95. If $n_- = n_+$ further increase to 100, the expected lower confidence bound increase to 0.95, the expected lower confidence bound increases to 0.96.

In summary when SPC=0.5 and τ is less than 0.1, it is necessary to sample at least n_-=50 true negative chemicals to precisely estimate SPC. Positive predictivity is very low and negative predictivity is very high, each of which can be inferred based on n_- and n_+ equal to 10 or 25 chemicals but it requires 50 or more chemicals to estimate the parameters precisely.

Correlated Responses

The Monte Carlo sampling study and the resulting tables and figures were based on the assumption that the chemicals drawn from the population are independent of one another with respect to their reference status. That is the reference probability that a given chemical is positive is τ or the test assay probability is SNS irrespective of the reference toxicity status of the other chemicals in the sample.

In some situations the population can be divided into families such that the chemicals within a family would be expected to be more similar to one another with respect to reference toxicity status than chemicals that were drawn from different families. For example a family might consist of a subclass of chemicals with related chemical structure. In general the presence of dependence among chemicals degrades the inference precision relative to that from independent chemicals. It results in a reduced effective sample size.

Let F denote the family (i.e. chemical subclass) from which the chemical was drawn. Suppose that the probability that the chemical is positive given that it was drawn from family F = f is denoted by π_f. The families F chosen for the sample are assumed to be random, so $\{\pi_F\}$ are also random variables. Assume that the mean and variance of π_F are

$$E(\pi_F) = \tau$$
$$\mathrm{Var}(\pi_F) = \phi\ \tau(1-\tau) \qquad (0 \le \phi \le 1)$$

This expression for the mean and variance has the intuitively reasonably characteristic that the overall mean across all families is the overall proportion of positive chemicals, τ, and $\mathrm{Var}(\pi_F)$ is 0 if τ=0 or if τ=1. (Note that none of the values τ, ϕ, or π_F can be observed.)

If m chemicals are drawn from the same family, f, their overall average response

$$p_f \equiv (\sum X_i)/m$$

has mean τ and variance $[\tau(1-\tau)/m][1 + (m-1)\phi]$. The parameter ϕ can be considered a correlation among the chemicals from the same family. If $\phi=0$ the chemicals from the same family are m independent chemicals. If $\phi=1$ the chemicals from the same family are perfectly correlated and so there is an effective sample size of 1, irrespective of the number of chemicals sampled. In this situation all the chemicals from the family would either be positive or all would be negative.

In general the situation lies somewhere in between. The effect of positive correlation is to increase the increase the variability of the estimates relative to what it would be if the chemicals were independent. This reduces the effective sample size so that the estimation precision obtained from say 50 correlated chemicals might be no more than that which would obtained from say 20 uncorrelated chemicals.

The effective sample size of independent chemicals, m_{eff}, corresponding to sampling m chemicals with correlation ϕ can be calculated by equating the variance expressions. Namely

$$[\tau(1-\tau)]/m_{eff} = [1 + (m-1)\phi]\ [\tau(1-\tau)]/m$$

this implies that

$$\mathbf{m_{eff} = m/[1 + (m-1)\phi]}$$

For example if m=50 and $\phi = 0.10$ then $m_{eff} = 50/5.9 = 8.5 \approx 10$.

To get an intuitive feeling for the anticipated extent of degradation in effective sample size due to correlation among the chemicals, assume that a sample of n_+ chemicals is drawn from the subpopulation of chemicals with positive reference status. Assume that the sample contains 5 chemicals from each of 10 subfamilies, with correlation $\phi=0.5$ within each subfamily and independence among different subfamilies. An average correlation among the $n_+ =50$ chemicals can approximated as 0.5 among the $10\times[(5\times4)/2]$ pairs of chemicals from the same family relative to the total of $[(50\times49/2]$ pairs among the 50 chemicals. Then ϕ_{avg} would be calculated as

$$\phi_{avg} = 0.5\times\{10\times[(5\times4)/2]\}/[(50\times49/2] = 0.04$$

Entering the expression for m_{eff} with m=50, $\phi_{avg} = 0.04$ yields $m_{eff} = 50/2.96 = 16.9 \approx 17$. Thus estimated inference sensitivity based on this sample of $n_+ = 50$ correlated chemicals would be based on the table and figure entries midway between $n_+ = 10$ and $n_+ = 25$.

DISCUSSION

This report discusses the results of a Monte Carlo study to estimate the inference sensitivity concerning the performance of a test assay as compared to a reference assay, that can be obtained from samples of various numbers and mixes of reference positive and reference negative chemicals. The precision of the assay is expressed in terms of Cooper statistics. Estimates of the precision of inferences about the Cooper statistics are presented in a series of tables and figures which show trends as a function of the numbers of reference positive and reference negative sampled chemicals vary.

The Monte Carlo study results suggest that it is important to have reasonable sized samples, n_+ and n_-, of both the positive and negative chemicals. This is because the inference precision for both the sensitivity and negative predictivity parameters depend primarily on n_+, whereas the inference precision for the specificity and positive predictivity parameters depend mostly on n_-.

It does not appear that sampling one to two dozen chemicals will produce precise inferences about the Cooper statistics.

Two situations were considered, one where both the sensitivity and specificity for the test assay are relatively high and the other where the specificity is low. In either case the sensitivity and specificity parameters cannot be precisely determined based on just n_+ and n_- equal to 10 or 25 chemicals. At least 50 to 100 chemicals in each category are need for precise determinations.

The positive predictivity is very low, particularly when the specificity is low. It further decreases as the proportion of true positives decreases. Precise inferences about positive predictivity require at least $n_-=100$ negative chemicals. Thus the test assay must be regarded as an initial screen which is expected to predict many false positives. One cannot declare a chemical to be positive solely on the basis of this test assay.

Negative predictivity is very high and increases as the proportion of true positives decreases. Negative predictivity can be determined to be high based on just $n_+ = n_- =10$ chemicals but at least $n_+ = n_- =25$ are required in order to obtain precise estimates.

The tables and figures in report as well as the majority of the discussion assume that the sampled chemicals are random samples from the set of all reference positive and the set of all reference negative chemicals. Correlations among the sampled chemicals, e.g. by selecting the sampled chemicals from the same chemical subclasses, will degrade the inference precision. An approximate expression is given to convert a sample size with correlated observations to a reduced “effective” sample size of independent chemicals. This permits estimates of inference sensitivity to be obtained from the results presented in the tables and figures. The estimates of inference precision given in this report, based on the assumption of independent chemicals, thus represent upper bounds on the inference precision that would be expected to be actually obtained

from samples of chemicals.

Reference

Cooper, J.A., Saracci, R., and Cole, P. (1979). Describing the validity of carcinogen screening tests. *British Journal of Cancer* **39**, 87-89.

Table 1. Means, Standard Deviations, and 95% Confidence Intervals for Cooper Statistics. Alternative Numbers of Positive (N1) and Negative (N2) Reference Chemicals. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.10.

		Sensitivity(=0.9)		Specificity(=0.9)		Pos. Pred.(=0.500)		Neg Pred.(=0.988)	
N1	N2	Mean (Std)	95% CI	Mean (Std)	95% CI	Mean (Std)	95% CI	Mean (Std)	95% CI
10	10	0.900(0.096)	(0.700, 1.000)	0.901(0.092)	(0.700, 1.000)	0.622(0.287)	(0.250, 1.000)	0.988(0.012)	(0.960, 1.000)
	25	0.900(0.096)	(0.700, 1.000)	0.901(0.058)	(0.760, 1.000)	0.549(0.175)	(0.294, 1.000)	0.988(0.012)	(0.962, 1.000)
	50	0.900(0.096)	(0.700, 1.000)	0.901(0.041)	(0.820, 0.980)	0.524(0.118)	(0.333, 0.833)	0.988(0.012)	(0.963, 1.000)
	100	0.900(0.096)	(0.700, 1.000)	0.901(0.029)	(0.840, 0.950)	0.511(0.082)	(0.370, 0.690)	0.988(0.011)	(0.964, 1.000)
25	10	0.902(0.062)	(0.760, 1.000)	0.901(0.092)	(0.700, 1.000)	0.623(0.286)	(0.246, 1.000)	0.988(0.008)	(0.973, 1.000)
	25	0.902(0.062)	(0.760, 1.000)	0.901(0.058)	(0.760, 1.000)	0.550(0.174)	(0.299, 1.000)	0.988(0.007)	(0.972, 1.000)
	50	0.902(0.062)	(0.760, 1.000)	0.901(0.041)	(0.820, 0.980)	0.525(0.116)	(0.341, 0.830)	0.988(0.007)	(0.973, 1.000)
	100	0.902(0.062)	(0.760, 1.000)	0.901(0.029)	(0.840, 0.950)	0.513(0.080)	(0.377, 0.681)	0.988(0.007)	(0.972, 1.000)
50	10	0.901(0.043)	(0.820, 0.980)	0.901(0.092)	(0.700, 1.000)	0.623(0.286)	(0.246, 1.000)	0.988(0.005)	(0.976, 0.998)
	25	0.901(0.043)	(0.820, 0.980)	0.901(0.058)	(0.760, 1.000)	0.550(0.174)	(0.303, 1.000)	0.988(0.005)	(0.977, 0.997)
	50	0.901(0.043)	(0.820, 0.980)	0.901(0.041)	(0.820, 0.980)	0.525(0.116)	(0.347, 0.833)	0.988(0.005)	(0.977, 0.997)
	100	0.901(0.043)	(0.820, 0.980)	0.901(0.029)	(0.840, 0.950)	0.513(0.079)	(0.379, 0.681)	0.988(0.005)	(0.977, 0.997)
100	10	0.901(0.031)	(0.840, 0.960)	0.901(0.092)	(0.700, 1.000)	0.623(0.286)	(0.246, 1.000)	0.988(0.004)	(0.980, 0.994)
	25	0.901(0.031)	(0.840, 0.960)	0.901(0.058)	(0.760, 1.000)	0.550(0.174)	(0.300, 1.000)	0.988(0.004)	(0.980, 0.995)
	50	0.901(0.031)	(0.840, 0.960)	0.901(0.041)	(0.820, 0.980)	0.525(0.116)	(0.348, 0.833)	0.988(0.004)	(0.980, 0.995)
	100	0.901(0.031)	(0.840, 0.960)	0.901(0.029)	(0.840, 0.950)	0.513(0.078)	(0.382, 0.676)	0.988(0.004)	(0.981, 0.995)

Table 2. Means, Standard Deviations, and 95% Confidence Intervals for Cooper Statistics. Alternative Numbers of Positive (N1) and Negative (N2) Reference Chemicals. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.05.

		Sensitivity(=0.9)		Specificity(=0.9)		Pos. Pred.(=0.321)		Neg Pred.(=0.994)	
N1	N2	Mean (Std)	95% CI	Mean (Std)	95% CI	Mean (Std)	95% CI	Mean (Std)	95% CI
10	10	0.900(0.096)	(0.700, 1.000)	0.901(0.092)	(0.700, 1.000)	0.518(0.357)	(0.136, 1.000)	0.994(0.006)	(0.981, 1.000)
	25	0.900(0.096)	(0.700, 1.000)	0.901(0.058)	(0.760, 1.000)	0.392(0.202)	(0.165, 1.000)	0.994(0.006)	(0.982, 1.000)
	50	0.900(0.096)	(0.700, 1.000)	0.901(0.041)	(0.820, 0.980)	0.353(0.121)	(0.191, 0.703)	0.994(0.006)	(0.982, 1.000)
	100	0.900(0.096)	(0.700, 1.000)	0.901(0.029)	(0.840, 0.950)	0.336(0.077)	(0.218, 0.513)	0.994(0.006)	(0.982, 1.000)
25	10	0.902(0.062)	(0.760, 1.000)	0.901(0.092)	(0.700, 1.000)	0.518(0.356)	(0.134, 1.000)	0.994(0.004)	(0.987, 1.000)
	25	0.902(0.062)	(0.760, 1.000)	0.901(0.058)	(0.760, 1.000)	0.392(0.202)	(0.168, 1.000)	0.994(0.004)	(0.986, 1.000)
	50	0.902(0.062)	(0.760, 1.000)	0.901(0.041)	(0.820, 0.980)	0.354(0.120)	(0.197, 0.698)	0.994(0.004)	(0.987, 1.000)
	100	0.902(0.062)	(0.760, 1.000)	0.901(0.029)	(0.840, 0.950)	0.337(0.075)	(0.223, 0.503)	0.994(0.004)	(0.987, 1.000)
50	10	0.901(0.043)	(0.820, 0.980)	0.901(0.092)	(0.700, 1.000)	0.518(0.356)	(0.134, 1.000)	0.994(0.003)	(0.988, 0.999)
	25	0.901(0.043)	(0.820, 0.980)	0.901(0.058)	(0.760, 1.000)	0.392(0.201)	(0.171, 1.000)	0.994(0.003)	(0.989, 0.999)
	50	0.901(0.043)	(0.820, 0.980)	0.901(0.041)	(0.820, 0.980)	0.354(0.120)	(0.201, 0.703)	0.994(0.003)	(0.989, 0.999)
	100	0.901(0.043)	(0.820, 0.980)	0.901(0.029)	(0.840, 0.950)	0.337(0.074)	(0.224, 0.503)	0.994(0.003)	(0.989, 0.999)
100	10	0.901(0.031)	(0.840, 0.960)	0.901(0.092)	(0.700, 1.000)	0.518(0.356)	(0.134, 1.000)	0.994(0.002)	(0.990, 0.997)
	25	0.901(0.031)	(0.840, 0.960)	0.901(0.058)	(0.760, 1.000)	0.393(0.201)	(0.169, 1.000)	0.994(0.002)	(0.991, 0.997)
	50	0.901(0.031)	(0.840, 0.960)	0.901(0.041)	(0.820, 0.980)	0.354(0.120)	(0.202, 0.703)	0.994(0.002)	(0.991, 0.997)
	100	0.901(0.031)	(0.840, 0.960)	0.901(0.029)	(0.840, 0.950)	0.337(0.074)	(0.226, 0.497)	0.994(0.002)	(0.991, 0.998)

Table 3. Means, Standard Deviations, and 95% Confidence Intervals for Cooper Statistics. Alternative Numbers of Positive (N1) and Negative (N2) Reference Chemicals. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.01.

N1	N2	Sensitivity(=0.9) Mean (Std)	95% CI	Specificity(=0.9) Mean (Std)	95% CI	Pos. Pred.(=0.083) Mean (Std)	95% CI	Neg Pred.(=0.999) Mean (Std)	95% CI
10	10	0.900(0.096)	(0.700, 1.000)	0.901(0.092)	(0.700, 1.000)	0.390(0.446)	(0.029, 1.000)	0.999(0.001)	(0.996, 1.000)
	25	0.900(0.096)	(0.700, 1.000)	0.901(0.058)	(0.760, 1.000)	0.161(0.234)	(0.036, 1.000)	0.999(0.001)	(0.996, 1.000)
	50	0.900(0.096)	(0.700, 1.000)	0.901(0.041)	(0.820, 0.980)	0.106(0.094)	(0.043, 0.312)	0.999(0.001)	(0.996, 1.000)
	100	0.900(0.096)	(0.700, 1.000)	0.901(0.029)	(0.840, 0.950)	0.091(0.033)	(0.051, 0.168)	0.999(0.001)	(0.997, 1.000)
25	10	0.902(0.062)	(0.760, 1.000)	0.901(0.092)	(0.700, 1.000)	0.390(0.445)	(0.029, 1.000)	0.999(0.001)	(0.997, 1.000)
	25	0.902(0.062)	(0.760, 1.000)	0.901(0.058)	(0.760, 1.000)	0.161(0.233)	(0.037, 1.000)	0.999(0.001)	(0.997, 1.000)
	50	0.902(0.062)	(0.760, 1.000)	0.901(0.041)	(0.820, 0.980)	0.106(0.094)	(0.045, 0.308)	0.999(0.001)	(0.997, 1.000)
	100	0.902(0.062)	(0.760, 1.000)	0.901(0.029)	(0.840, 0.950)	0.091(0.033)	(0.052, 0.162)	0.999(0.001)	(0.997, 1.000)
50	10	0.901(0.043)	(0.820, 0.980)	0.901(0.092)	(0.700, 1.000)	0.390(0.445)	(0.029, 1.000)	0.999(0.001)	(0.998, 1.000)
	25	0.901(0.043)	(0.820, 0.980)	0.901(0.058)	(0.760, 1.000)	0.161(0.233)	(0.038, 1.000)	0.999(0.000)	(0.998, 1.000)
	50	0.901(0.043)	(0.820, 0.980)	0.901(0.041)	(0.820, 0.980)	0.106(0.094)	(0.046, 0.312)	0.999(0.000)	(0.998, 1.000)
	100	0.901(0.043)	(0.820, 0.980)	0.901(0.029)	(0.840, 0.950)	0.091(0.032)	(0.053, 0.162)	0.999(0.000)	(0.998, 1.000)
100	10	0.901(0.031)	(0.840, 0.960)	0.901(0.092)	(0.700, 1.000)	0.390(0.445)	(0.029, 1.000)	0.999(0.000)	(0.998, 0.999)
	25	0.901(0.031)	(0.840, 0.960)	0.901(0.058)	(0.760, 1.000)	0.161(0.233)	(0.037, 1.000)	0.999(0.000)	(0.998, 1.000)
	50	0.901(0.031)	(0.840, 0.960)	0.901(0.041)	(0.820, 0.980)	0.106(0.094)	(0.046, 0.312)	0.999(0.000)	(0.998, 1.000)
	100	0.901(0.031)	(0.840, 0.960)	0.901(0.029)	(0.840, 0.950)	0.091(0.032)	(0.053, 0.160)	0.999(0.000)	(0.998, 1.000)

Table 4. Means, Standard Deviations, and 95% Confidence Intervals for Cooper Statistics. Alternative Numbers of Positive (N1) and Negative (N2) Reference Chemicals. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.10.

		Sensitivity(=0.9)		Specificity(=0.5)		Pos. Pred.(=0.167)		Neg Pred.(=0.978)	
N1	N2	Mean (Std)	95% CI	Mean (Std)	95% CI	Mean (Std)	95% CI	Mean (Std)	95% CI
10	10	0.900(0.096)	(0.700, 1.000)	0.496(0.155)	(0.200, 0.800)	0.179(0.060)	(0.100, 0.333)	0.975(0.041)	(0.900, 1.000)
	25	0.900(0.096)	(0.700, 1.000)	0.498(0.098)	(0.320, 0.680)	0.171(0.034)	(0.115, 0.258)	0.978(0.022)	(0.923, 1.000)
	50	0.900(0.096)	(0.700, 1.000)	0.499(0.069)	(0.360, 0.640)	0.168(0.025)	(0.122, 0.226)	0.978(0.021)	(0.926, 1.000)
	100	0.900(0.096)	(0.700, 1.000)	0.499(0.049)	(0.400, 0.600)	0.167(0.021)	(0.124, 0.207)	0.978(0.021)	(0.930, 1.000)
25	10	0.902(0.062)	(0.760, 1.000)	0.496(0.155)	(0.200, 0.800)	0.179(0.059)	(0.107, 0.338)	0.974(0.047)	(0.929, 1.000)
	25	0.902(0.062)	(0.760, 1.000)	0.498(0.098)	(0.320, 0.680)	0.171(0.032)	(0.122, 0.250)	0.978(0.015)	(0.947, 1.000)
	50	0.902(0.062)	(0.760, 1.000)	0.499(0.069)	(0.360, 0.640)	0.169(0.022)	(0.131, 0.219)	0.978(0.014)	(0.949, 1.000)
	100	0.902(0.062)	(0.760, 1.000)	0.499(0.049)	(0.400, 0.600)	0.168(0.017)	(0.137, 0.203)	0.979(0.013)	(0.950, 1.000)
50	10	0.901(0.043)	(0.820, 0.980)	0.496(0.155)	(0.200, 0.800)	0.179(0.058)	(0.109, 0.333)	0.974(0.046)	(0.938, 0.996)
	25	0.901(0.043)	(0.820, 0.980)	0.498(0.098)	(0.320, 0.680)	0.171(0.031)	(0.124, 0.246)	0.977(0.011)	(0.952, 0.996)
	50	0.901(0.043)	(0.820, 0.980)	0.499(0.069)	(0.360, 0.640)	0.169(0.021)	(0.134, 0.216)	0.978(0.010)	(0.956, 0.996)
	100	0.901(0.043)	(0.820, 0.980)	0.499(0.049)	(0.400, 0.600)	0.168(0.016)	(0.140, 0.200)	0.978(0.010)	(0.957, 0.996)
100	10	0.901(0.031)	(0.840, 0.960)	0.496(0.155)	(0.200, 0.800)	0.179(0.058)	(0.109, 0.335)	0.974(0.046)	(0.938, 0.991)
	25	0.901(0.031)	(0.840, 0.960)	0.498(0.098)	(0.320, 0.680)	0.171(0.030)	(0.124, 0.244)	0.977(0.009)	(0.957, 0.991)
	50	0.901(0.031)	(0.840, 0.960)	0.499(0.069)	(0.360, 0.640)	0.169(0.021)	(0.135, 0.216)	0.978(0.007)	(0.961, 0.991)
	100	0.901(0.031)	(0.840, 0.960)	0.499(0.049)	(0.400, 0.600)	0.168(0.015)	(0.142, 0.200)	0.978(0.007)	(0.963, 0.990)

Table 5. Means, Standard Deviations, and 95% Confidence Intervals for Cooper Statistics. Alternative Numbers of Positive (N1) and Negative (N2) Reference Chemicals. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.05.

N1	N2	Sensitivity(=0.9) Mean (Std)	95% CI	Specificity(=0.5) Mean (Std)	95% CI	Pos. Pred.(=0.087) Mean (Std)	95% CI	Neg Pred.(=0.990) Mean (Std)	95% CI
10	10	0.900(0.096)	(0.700, 1.000)	0.496(0.155)	(0.200, 0.800)	0.095(0.038)	(0.050, 0.191)	0.987(0.034)	(0.950, 1.000)
	25	0.900(0.096)	(0.700, 1.000)	0.498(0.098)	(0.320, 0.680)	0.089(0.020)	(0.058, 0.141)	0.989(0.011)	(0.962, 1.000)
	50	0.900(0.096)	(0.700, 1.000)	0.499(0.069)	(0.360, 0.640)	0.088(0.015)	(0.062, 0.122)	0.989(0.010)	(0.964, 1.000)
	100	0.900(0.096)	(0.700, 1.000)	0.499(0.049)	(0.400, 0.600)	0.087(0.012)	(0.063, 0.110)	0.990(0.010)	(0.966, 1.000)
25	10	0.902(0.062)	(0.760, 1.000)	0.496(0.155)	(0.200, 0.800)	0.095(0.037)	(0.054, 0.195)	0.986(0.045)	(0.965, 1.000)
	25	0.902(0.062)	(0.760, 1.000)	0.498(0.098)	(0.320, 0.680)	0.089(0.018)	(0.062, 0.136)	0.989(0.007)	(0.974, 1.000)
	50	0.902(0.062)	(0.760, 1.000)	0.499(0.069)	(0.360, 0.640)	0.088(0.013)	(0.067, 0.117)	0.990(0.007)	(0.975, 1.000)
	100	0.902(0.062)	(0.760, 1.000)	0.499(0.049)	(0.400, 0.600)	0.087(0.010)	(0.070, 0.107)	0.990(0.007)	(0.976, 1.000)
50	10	0.901(0.043)	(0.820, 0.980)	0.496(0.155)	(0.200, 0.800)	0.095(0.037)	(0.055, 0.191)	0.986(0.045)	(0.969, 0.998)
	25	0.901(0.043)	(0.820, 0.980)	0.498(0.098)	(0.320, 0.680)	0.089(0.018)	(0.063, 0.134)	0.989(0.005)	(0.977, 0.998)
	50	0.901(0.043)	(0.820, 0.980)	0.499(0.069)	(0.360, 0.640)	0.088(0.012)	(0.068, 0.116)	0.989(0.005)	(0.978, 0.998)
	100	0.901(0.043)	(0.820, 0.980)	0.499(0.049)	(0.400, 0.600)	0.087(0.009)	(0.071, 0.106)	0.990(0.005)	(0.979, 0.998)
100	10	0.901(0.031)	(0.840, 0.960)	0.496(0.155)	(0.200, 0.800)	0.095(0.036)	(0.055, 0.192)	0.986(0.045)	(0.969, 0.996)
	25	0.901(0.031)	(0.840, 0.960)	0.498(0.098)	(0.320, 0.680)	0.089(0.018)	(0.063, 0.133)	0.989(0.004)	(0.979, 0.996)
	50	0.901(0.031)	(0.840, 0.960)	0.499(0.069)	(0.360, 0.640)	0.088(0.012)	(0.069, 0.115)	0.989(0.004)	(0.981, 0.995)
	100	0.901(0.031)	(0.840, 0.960)	0.499(0.049)	(0.400, 0.600)	0.087(0.008)	(0.073, 0.106)	0.990(0.003)	(0.982, 0.995)

Table 6. Means, Standard Deviations, and 95% Confidence Intervals for Cooper Statistics. Alternative Numbers of Positive (N1) and Negative (N2) Reference Chemicals. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.01.

N1	N2	Sensitivity(=0.9) Mean (Std)	95% CI	Specificity(=0.5) Mean (Std)	95% CI	Pos. Pred.(=0.018) Mean (Std)	95% CI	Neg Pred.(=0.998) Mean (Std)	95% CI
10	10	0.900(0.096)	(0.700, 1.000)	0.496(0.155)	(0.200, 0.800)	0.020(0.009)	(0.010, 0.043)	0.997(0.032)	(0.990, 1.000)
	25	0.900(0.096)	(0.700, 1.000)	0.498(0.098)	(0.320, 0.680)	0.019(0.004)	(0.012, 0.031)	0.998(0.002)	(0.992, 1.000)
	50	0.900(0.096)	(0.700, 1.000)	0.499(0.069)	(0.360, 0.640)	0.018(0.003)	(0.012, 0.026)	0.998(0.002)	(0.993, 1.000)
	100	0.900(0.096)	(0.700, 1.000)	0.499(0.049)	(0.400, 0.600)	0.018(0.003)	(0.013, 0.023)	0.998(0.002)	(0.993, 1.000)
25	10	0.902(0.062)	(0.760, 1.000)	0.496(0.155)	(0.200, 0.800)	0.020(0.009)	(0.011, 0.044)	0.996(0.045)	(0.993, 1.000)
	25	0.902(0.062)	(0.760, 1.000)	0.498(0.098)	(0.320, 0.680)	0.019(0.004)	(0.012, 0.029)	0.998(0.001)	(0.995, 1.000)
	50	0.902(0.062)	(0.760, 1.000)	0.499(0.069)	(0.360, 0.640)	0.018(0.003)	(0.014, 0.025)	0.998(0.001)	(0.995, 1.000)
	100	0.902(0.062)	(0.760, 1.000)	0.499(0.049)	(0.400, 0.600)	0.018(0.002)	(0.014, 0.023)	0.998(0.001)	(0.995, 1.000)
50	10	0.901(0.043)	(0.820, 0.980)	0.496(0.155)	(0.200, 0.800)	0.020(0.009)	(0.011, 0.043)	0.996(0.045)	(0.994, 1.000)
	25	0.901(0.043)	(0.820, 0.980)	0.498(0.098)	(0.320, 0.680)	0.019(0.004)	(0.013, 0.029)	0.998(0.001)	(0.995, 1.000)
	50	0.901(0.043)	(0.820, 0.980)	0.499(0.069)	(0.360, 0.640)	0.018(0.003)	(0.014, 0.025)	0.998(0.001)	(0.996, 1.000)
	100	0.901(0.043)	(0.820, 0.980)	0.499(0.049)	(0.400, 0.600)	0.018(0.002)	(0.015, 0.022)	0.998(0.001)	(0.996, 1.000)
100	10	0.901(0.031)	(0.840, 0.960)	0.496(0.155)	(0.200, 0.800)	0.020(0.009)	(0.011, 0.044)	0.996(0.045)	(0.994, 0.999)
	25	0.901(0.031)	(0.840, 0.960)	0.498(0.098)	(0.320, 0.680)	0.019(0.004)	(0.013, 0.029)	0.998(0.001)	(0.996, 0.999)
	50	0.901(0.031)	(0.840, 0.960)	0.499(0.069)	(0.360, 0.640)	0.018(0.003)	(0.014, 0.024)	0.998(0.001)	(0.996, 0.999)
	100	0.901(0.031)	(0.840, 0.960)	0.499(0.049)	(0.400, 0.600)	0.018(0.002)	(0.015, 0.022)	0.998(0.001)	(0.997, 0.999)

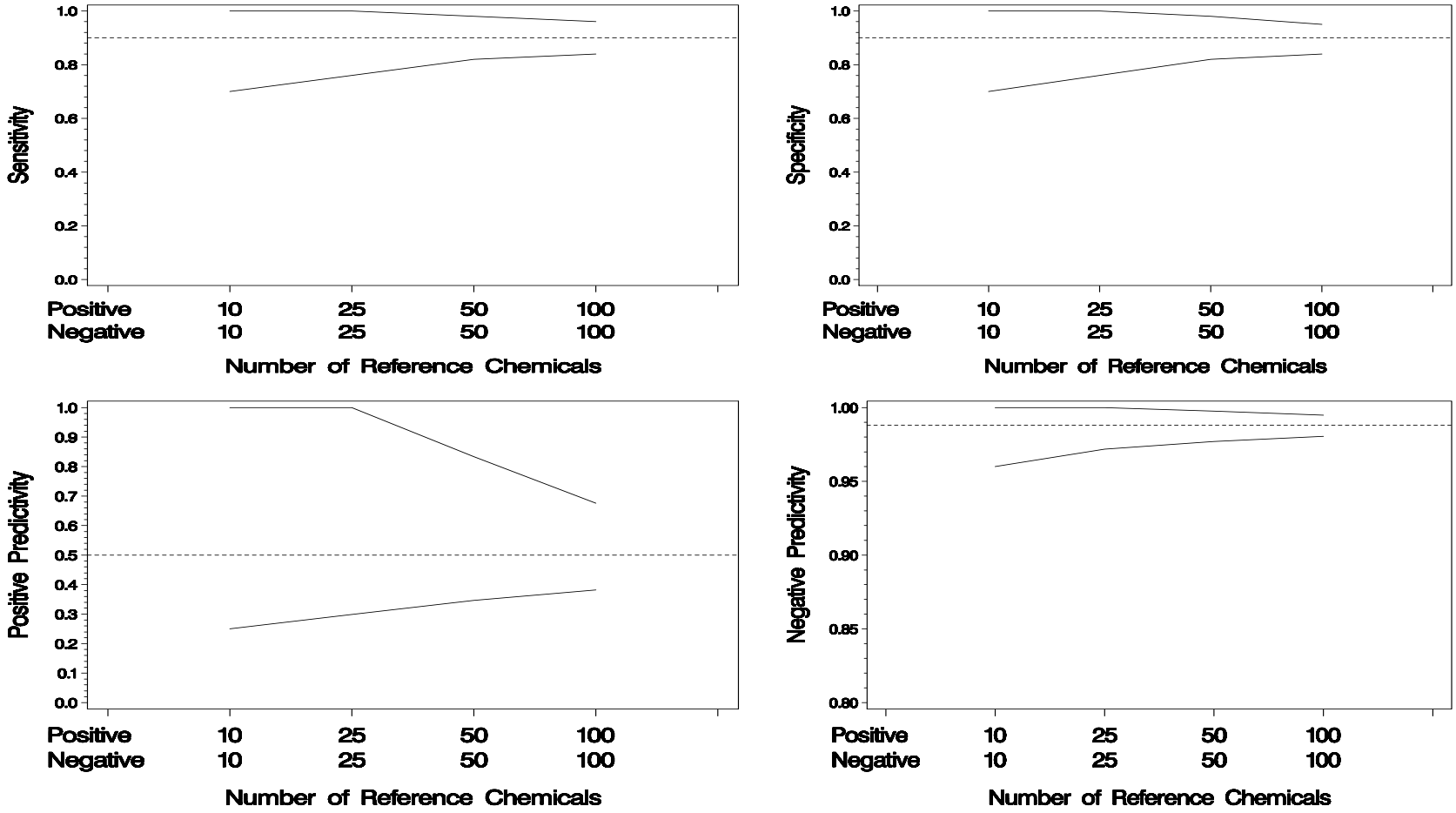
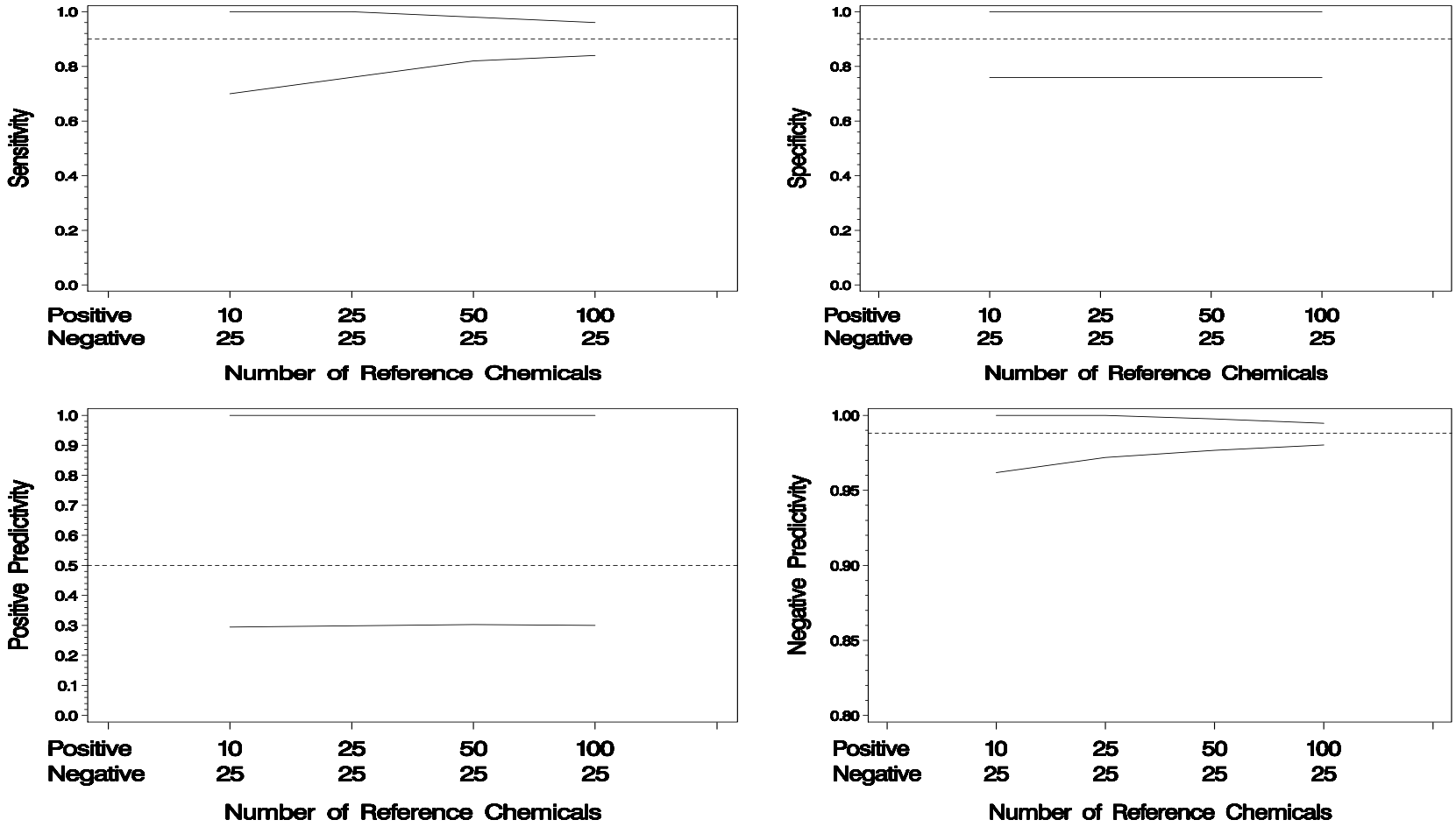
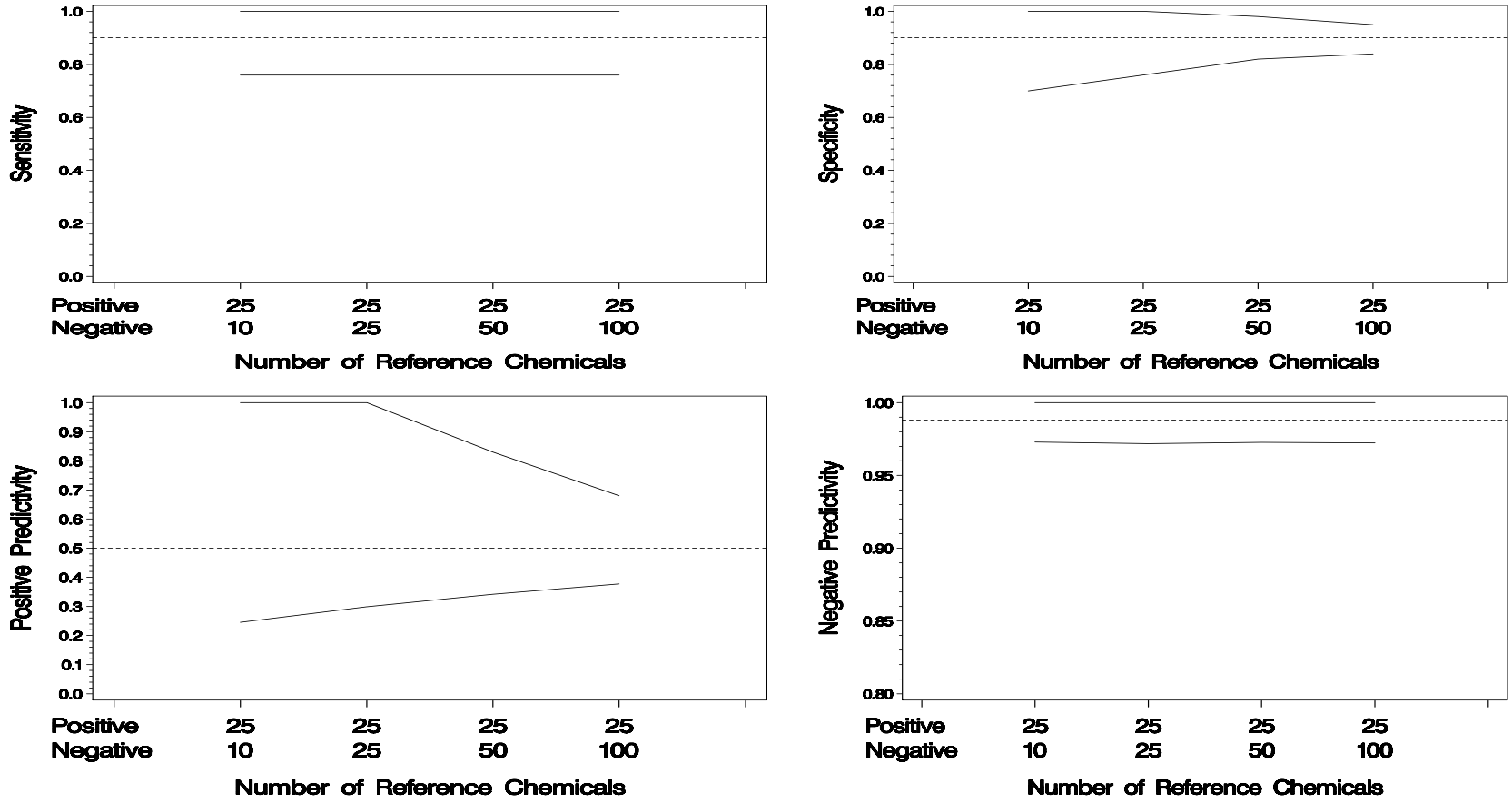


Figure 1-a. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive**



Reference=0.1. N1 = N2. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).

Figure 1-b. 95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference



Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.1. N2 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).

Figure 1-c. 95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.1. N1=25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).

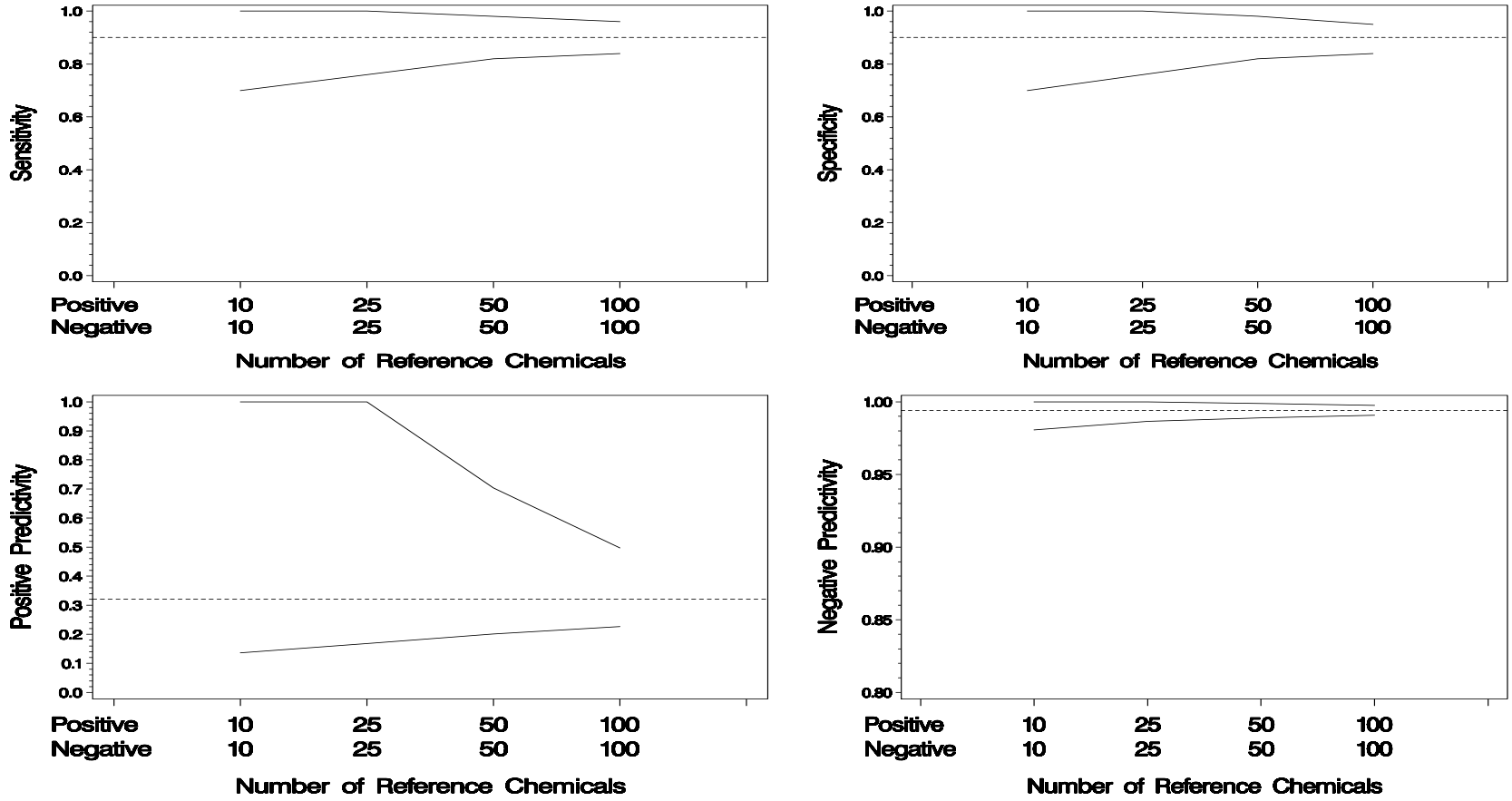


Figure 2-a. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.05. N1 = N2. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

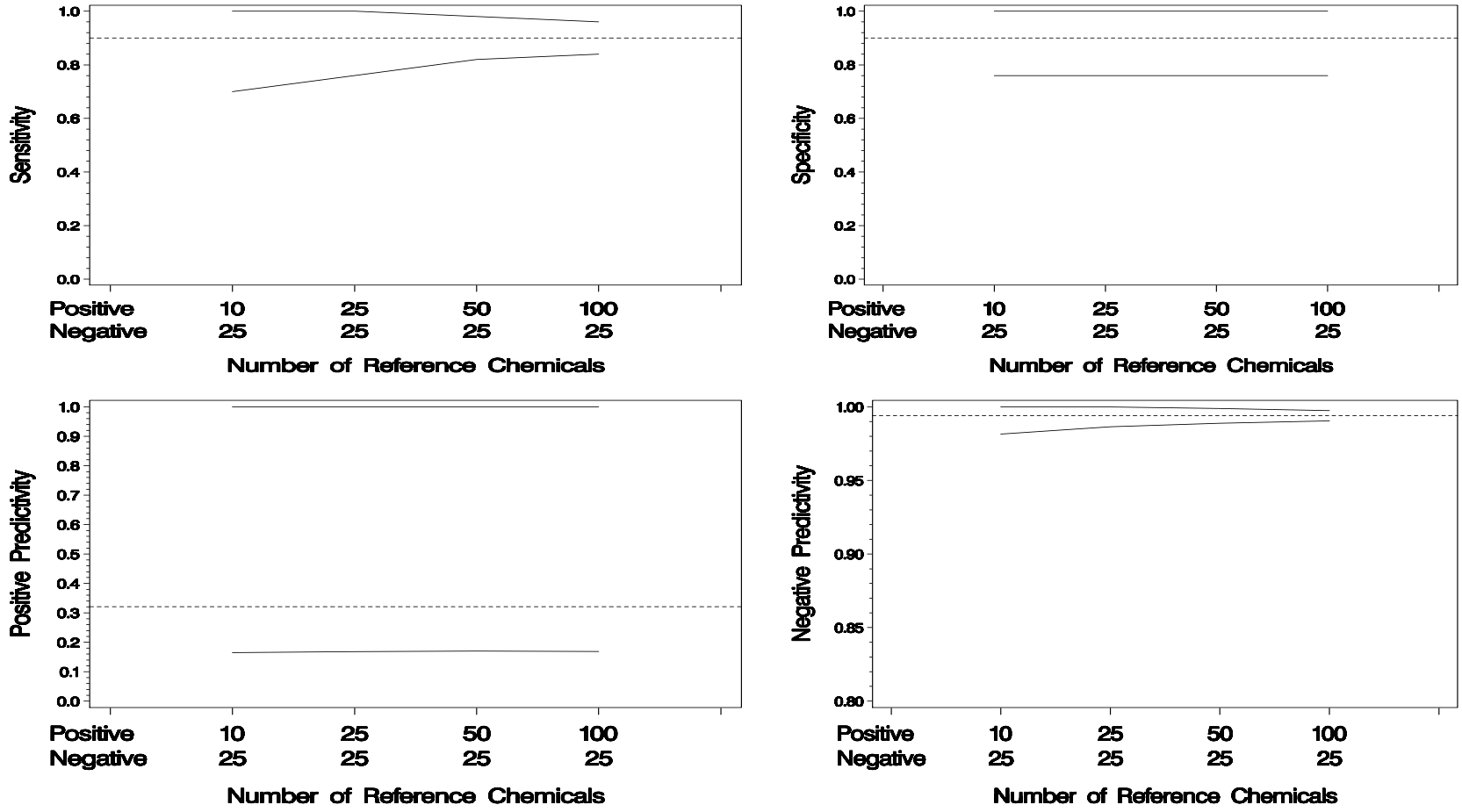


Figure 2-b. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.05. N2 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

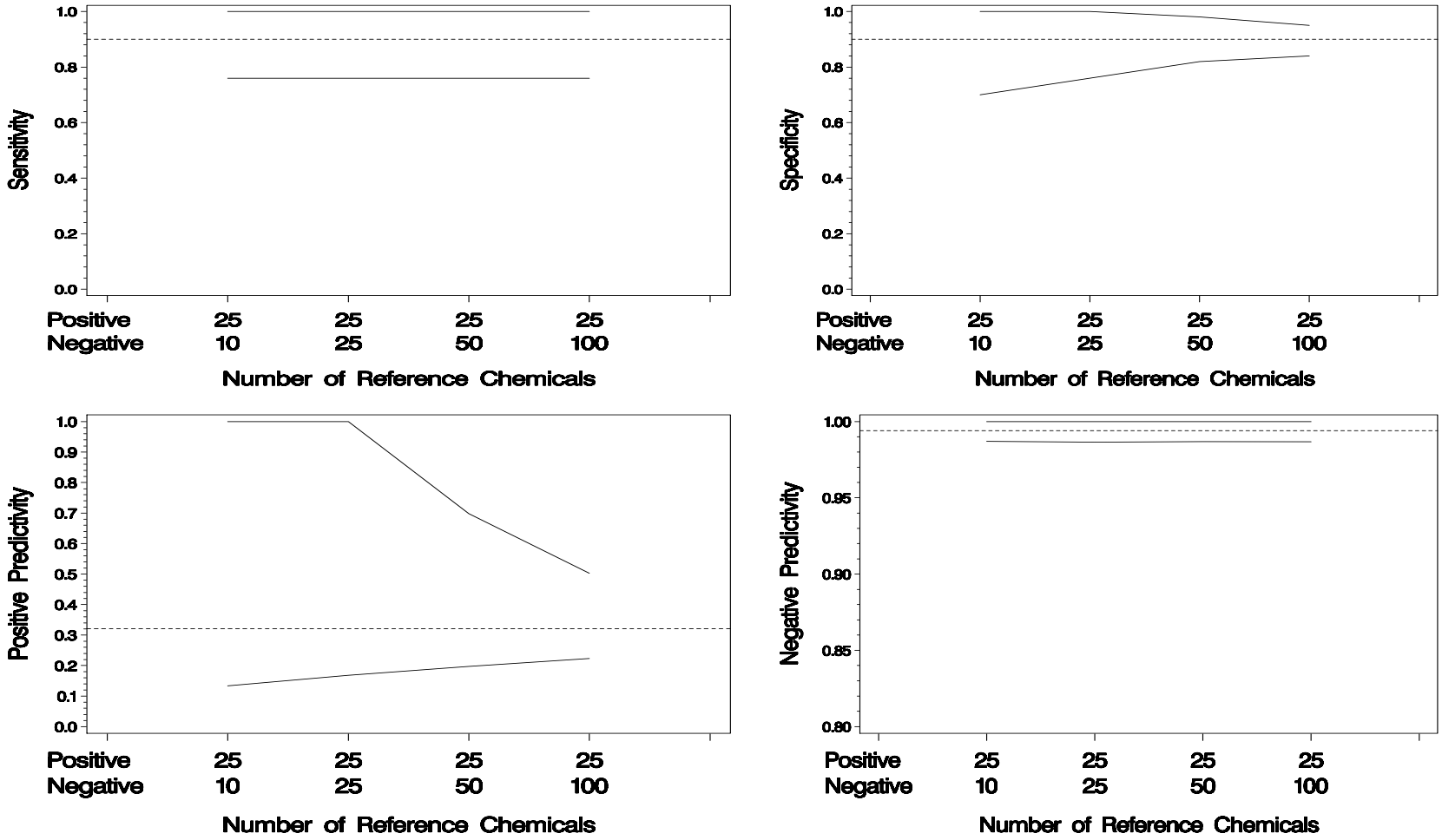


Figure 2-c. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.05. N1 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

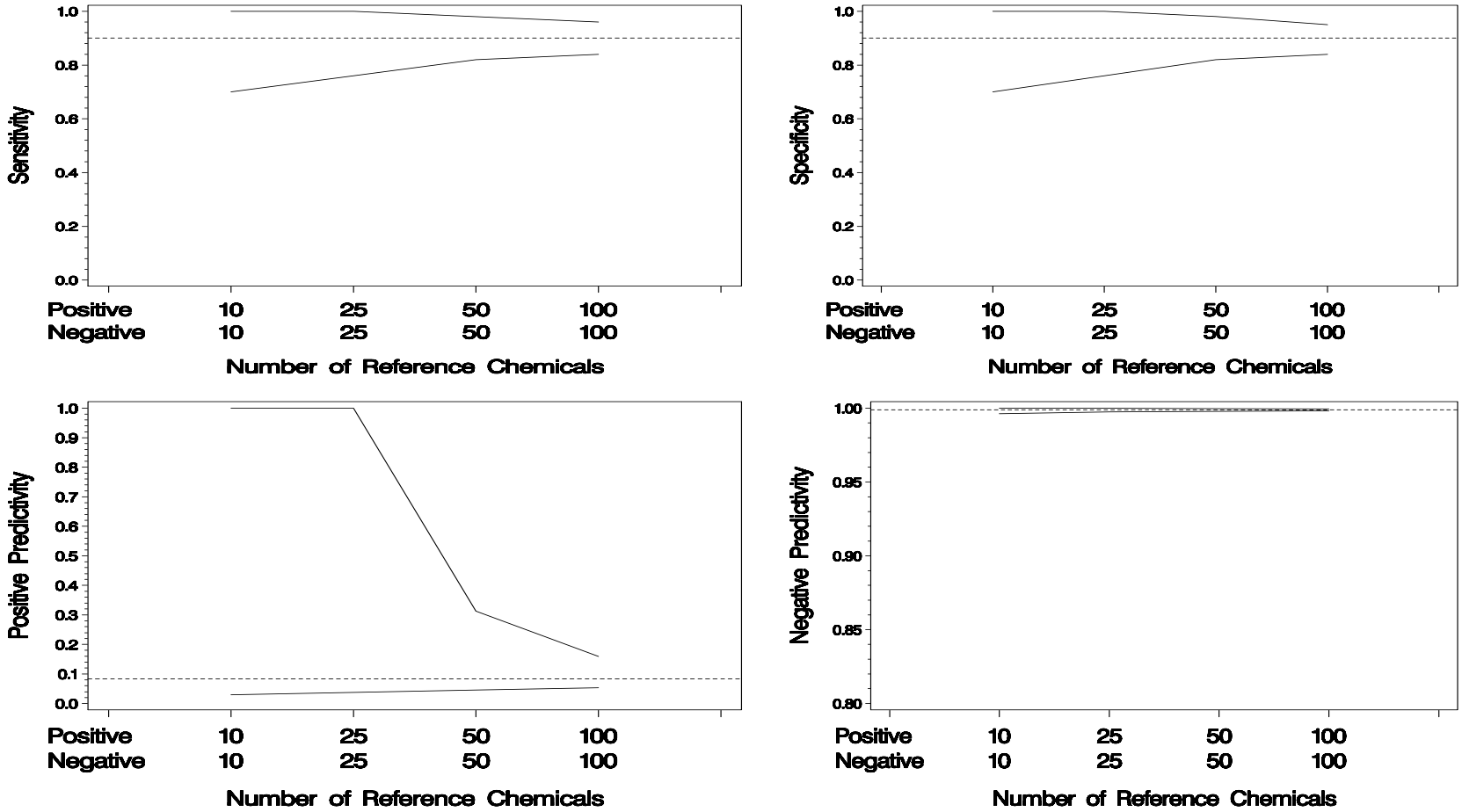
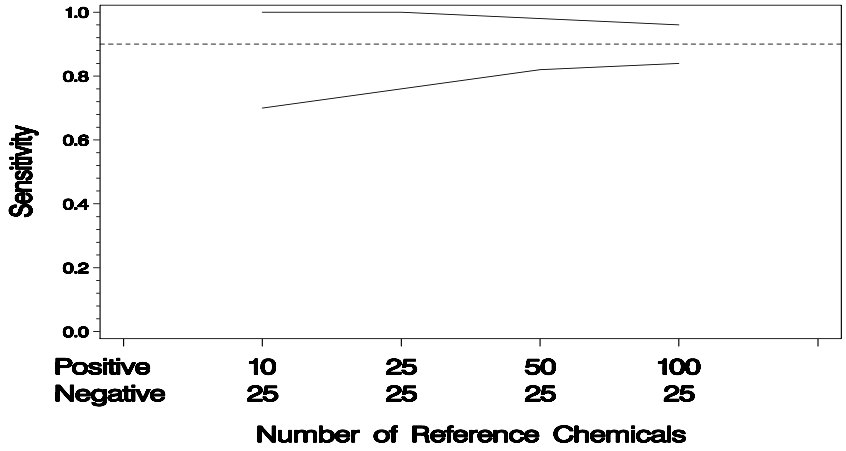
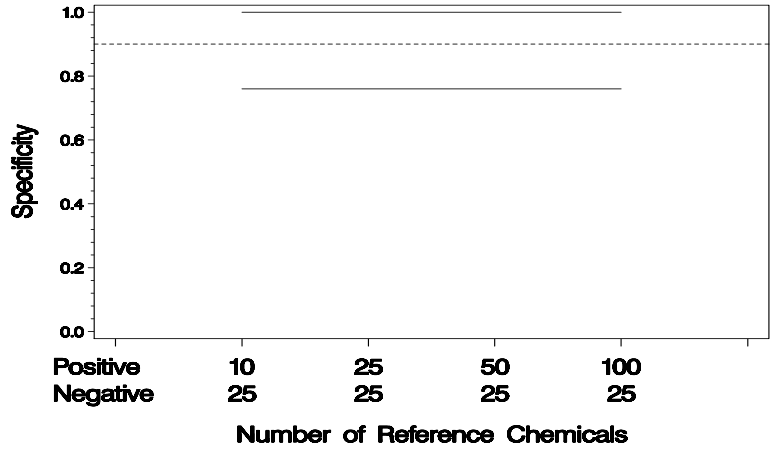
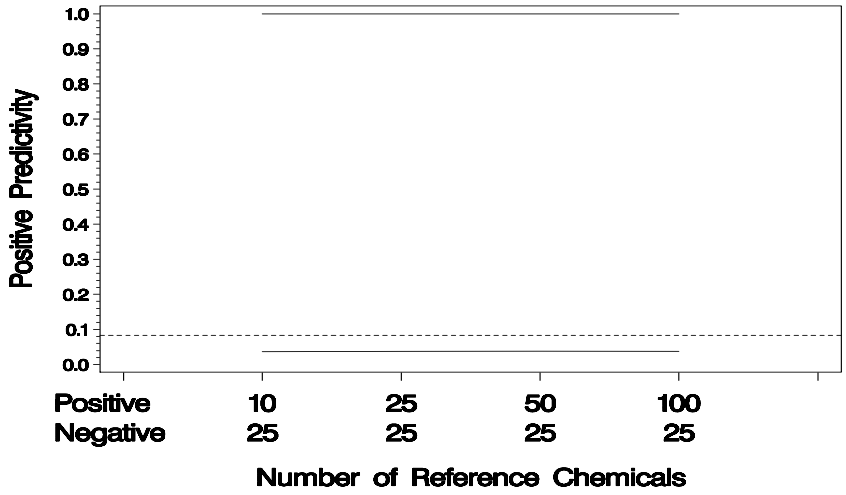
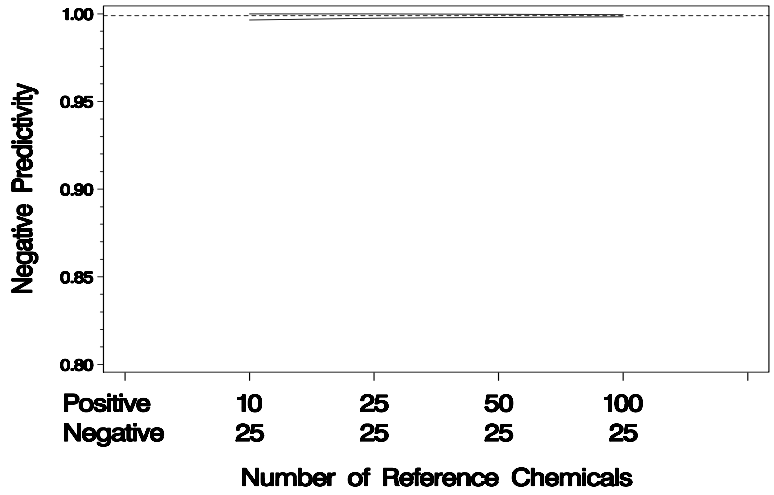


Figure 3-a. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.01. N1 = N2. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**


Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
Positive 10 25 50 100
Negative 25 25 25 25
Number of Reference Chemicals


Specificity
1.0
0.8
0.6
0.4
0.2
0.0
Positive 10 25 50 100
Negative 25 25 25 25
Number of Reference Chemicals


Positive Predictivity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Positive 10 25 50 100
Negative 25 25 25 25
Number of Reference Chemicals


Negative Predictivity
1.00
0.95
0.90
0.85
0.80
Positive 10 25 50 100
Negative 25 25 25 25
Number of Reference Chemicals

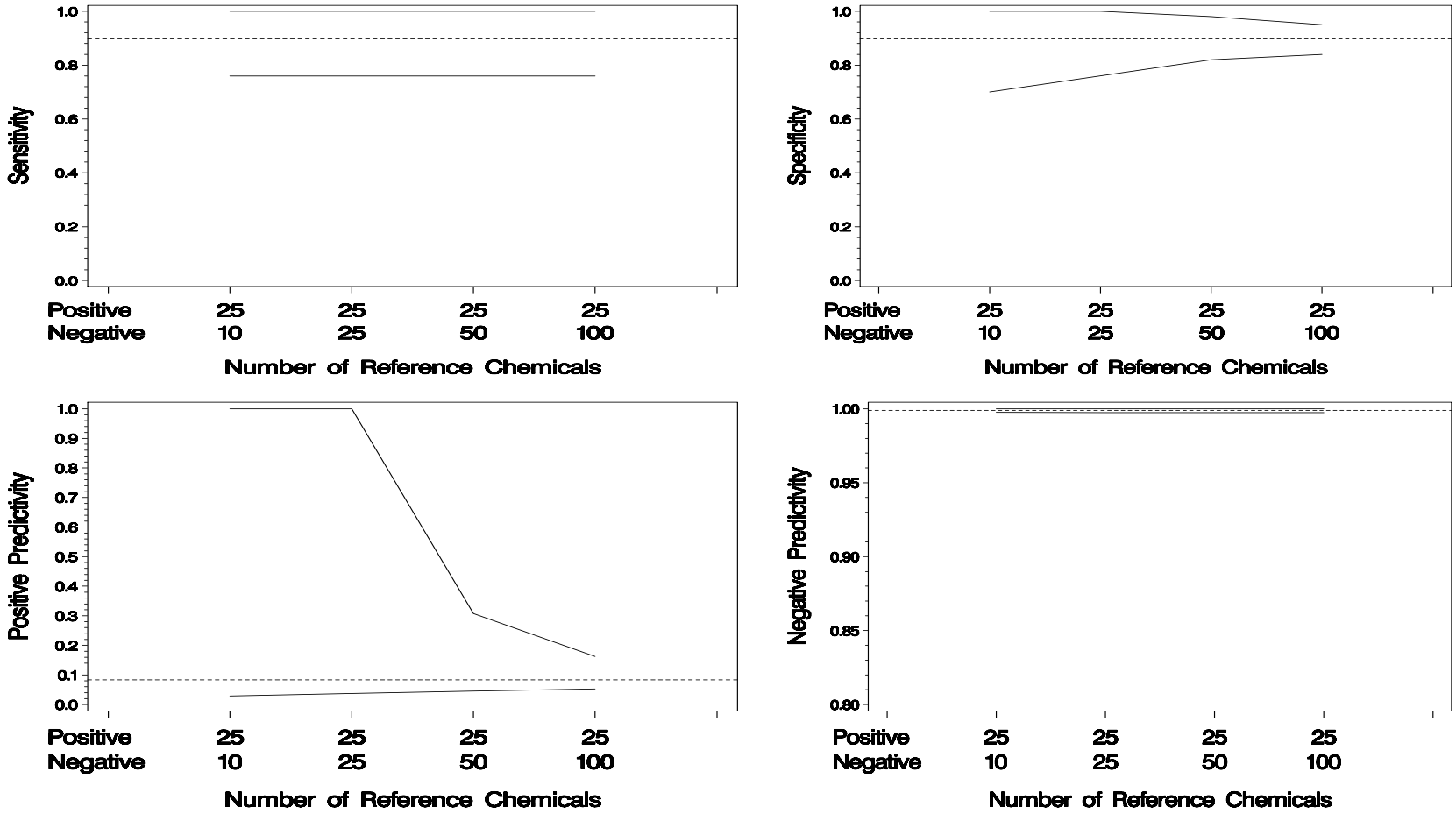


Figure 3-b. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.01. N2 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

Figure 3-c. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals.**

Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.01. N1 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).

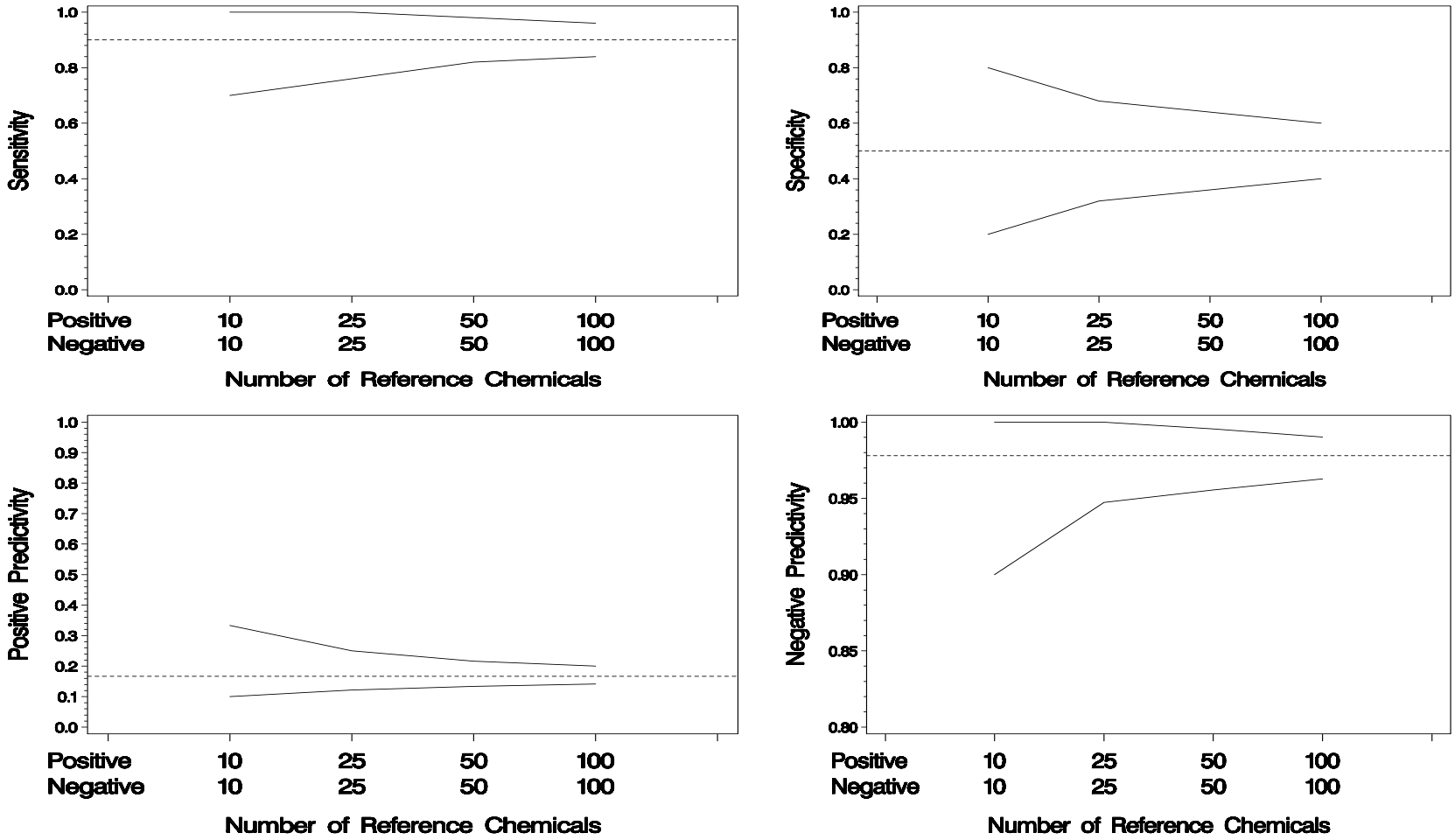


Figure 4-a. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.10. N1 = N2. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

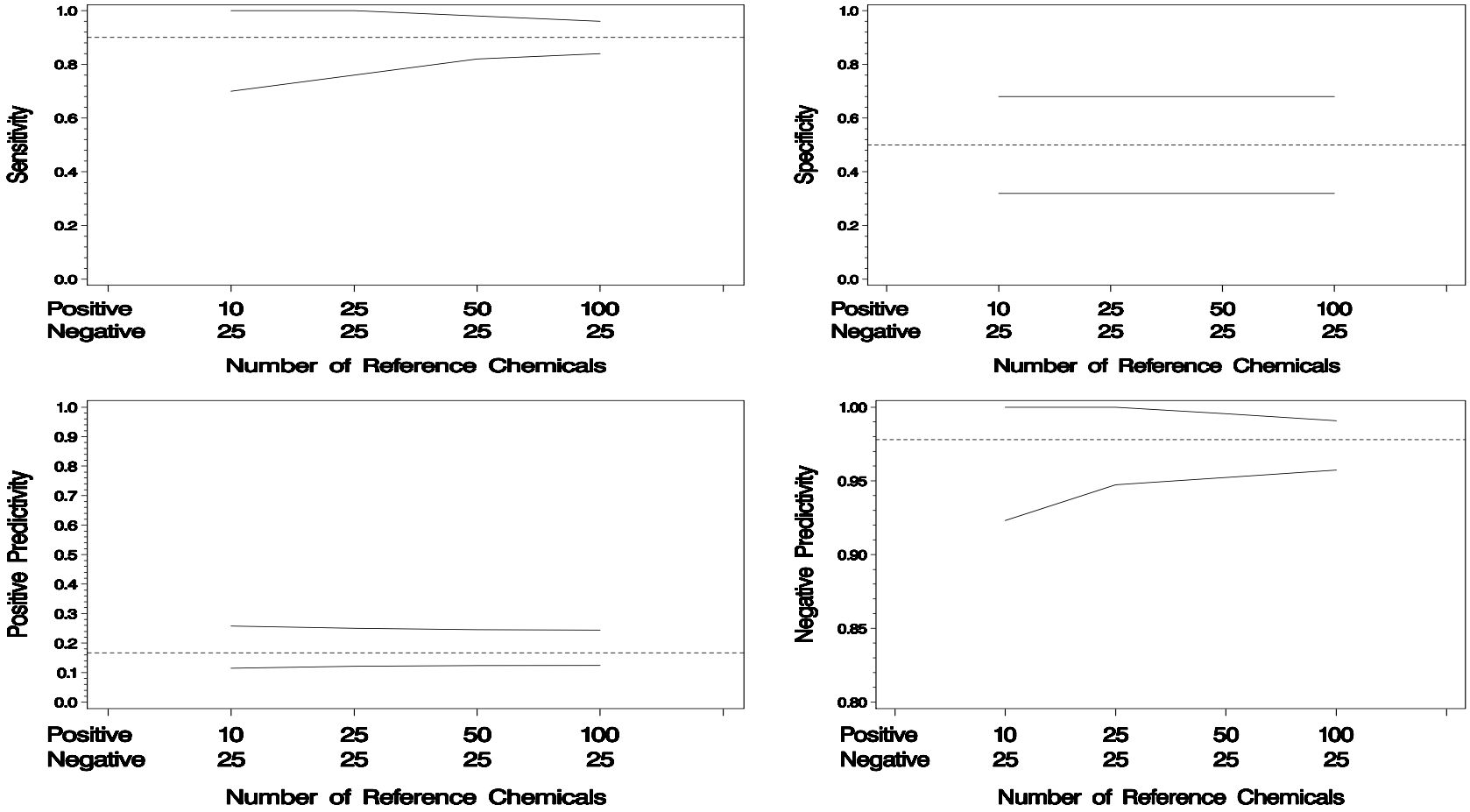


Figure 4-b. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.10. N2 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

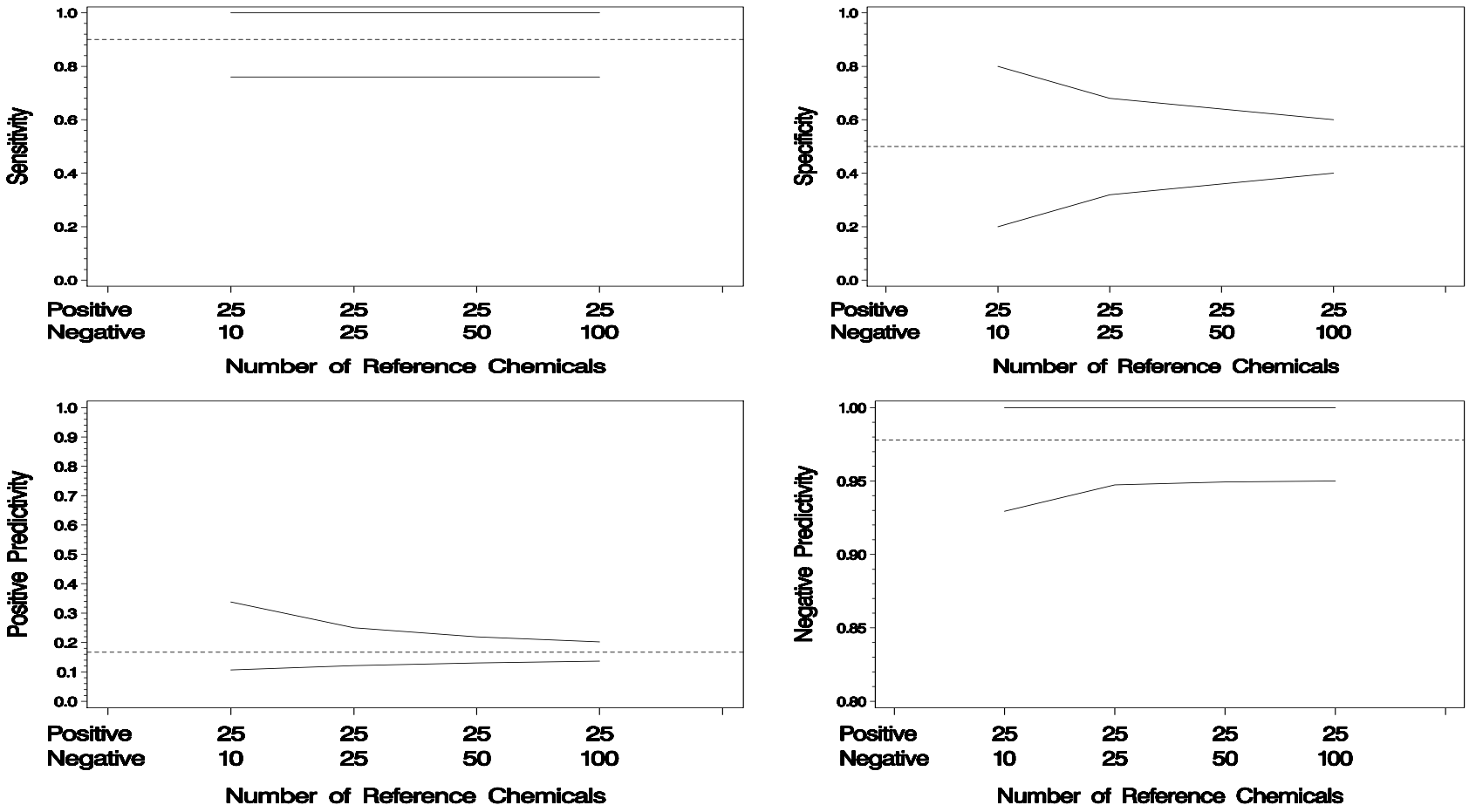


Figure 4-c. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.10. N1 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

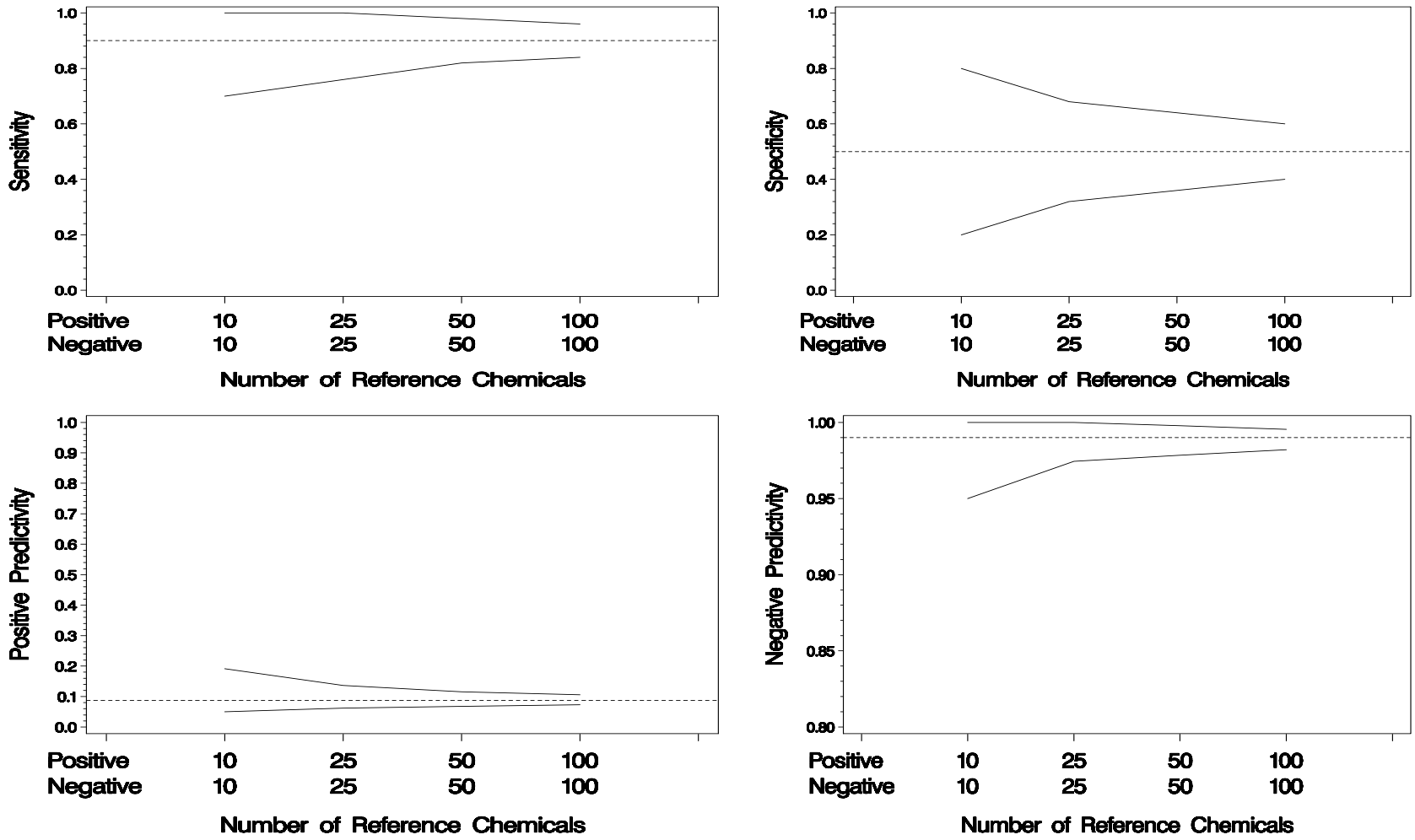


Figure 5-a. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.05. N1**

= N2. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).

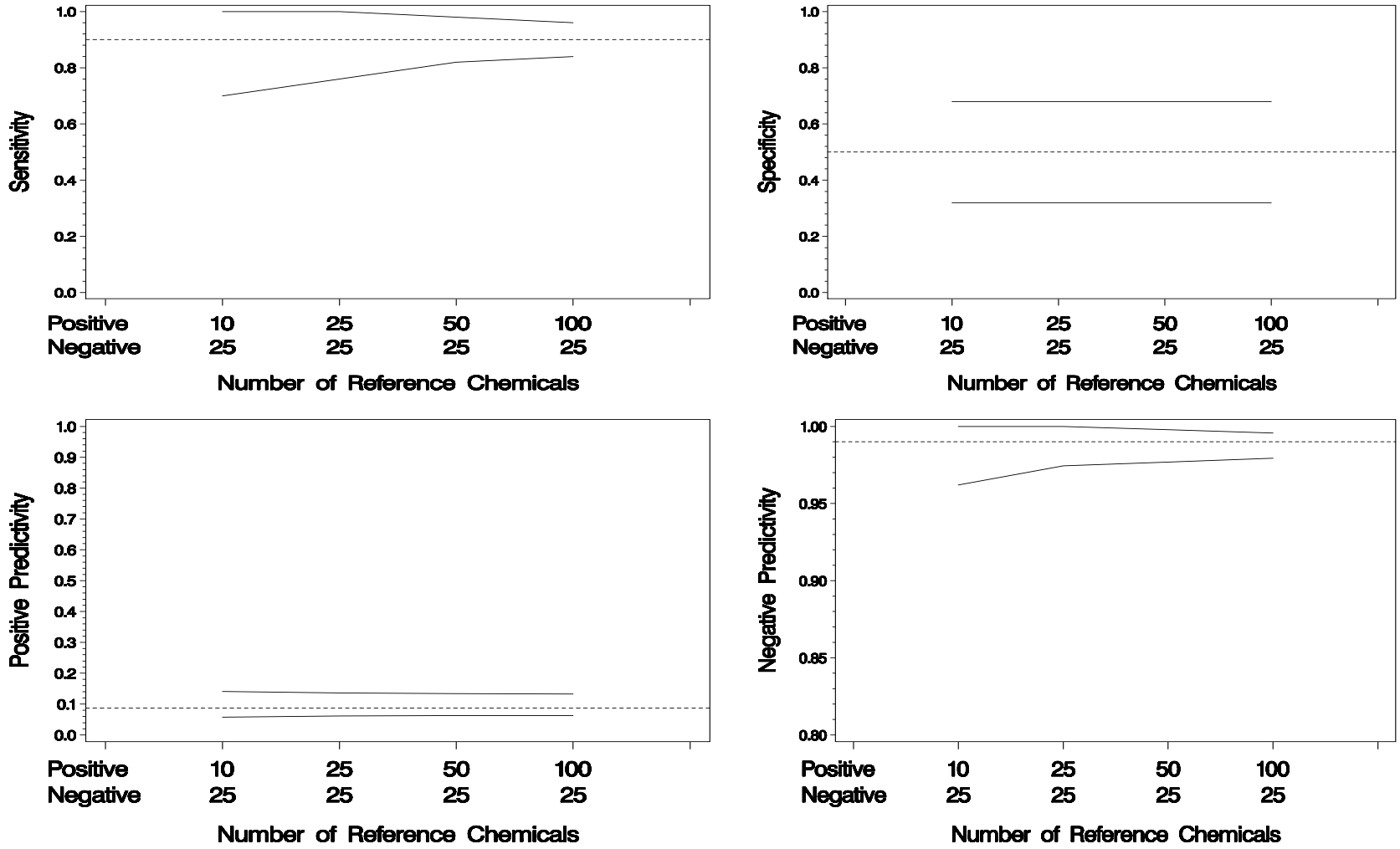


Figure 5-b. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.05. N2 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

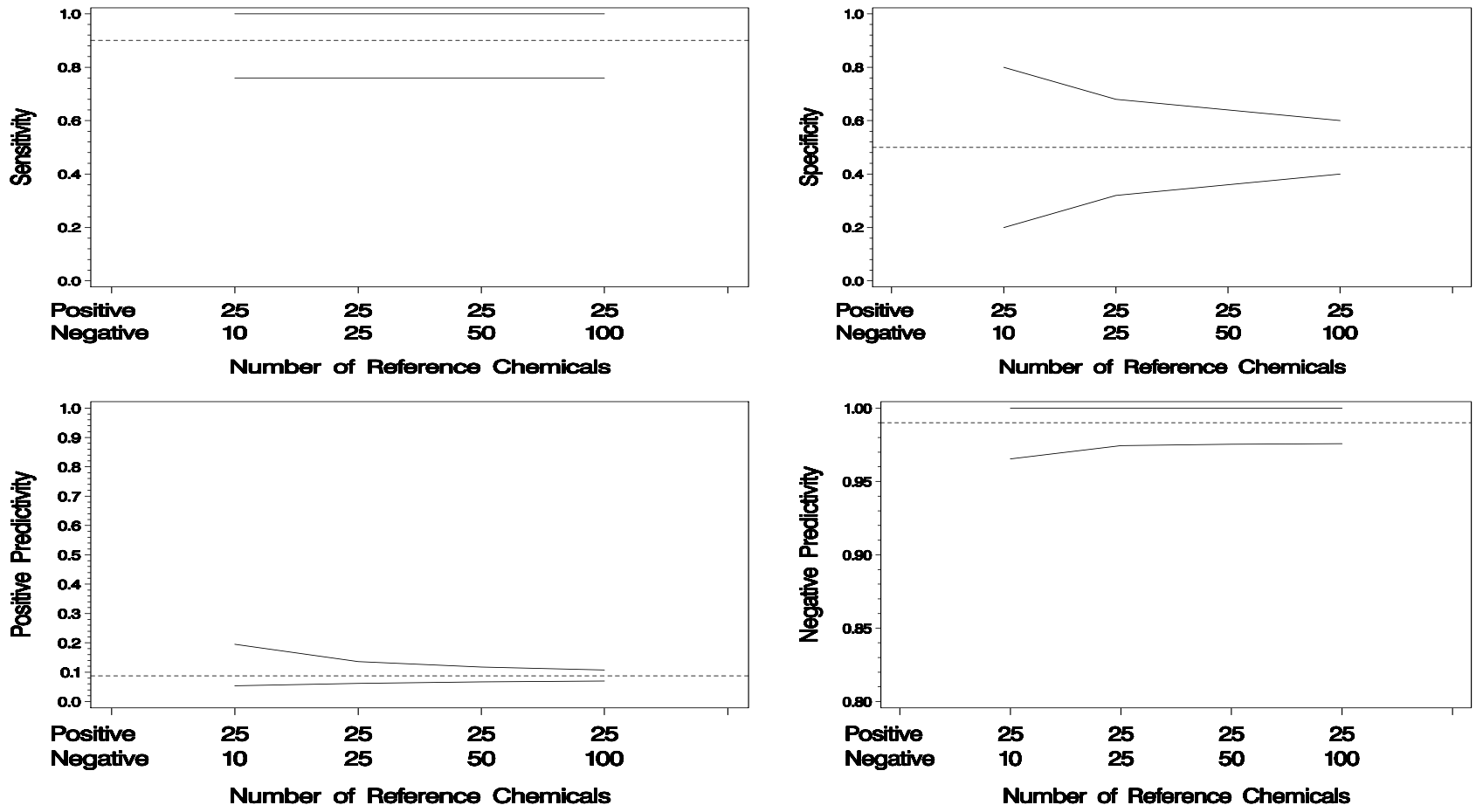


Figure 5-c. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.05. N1 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

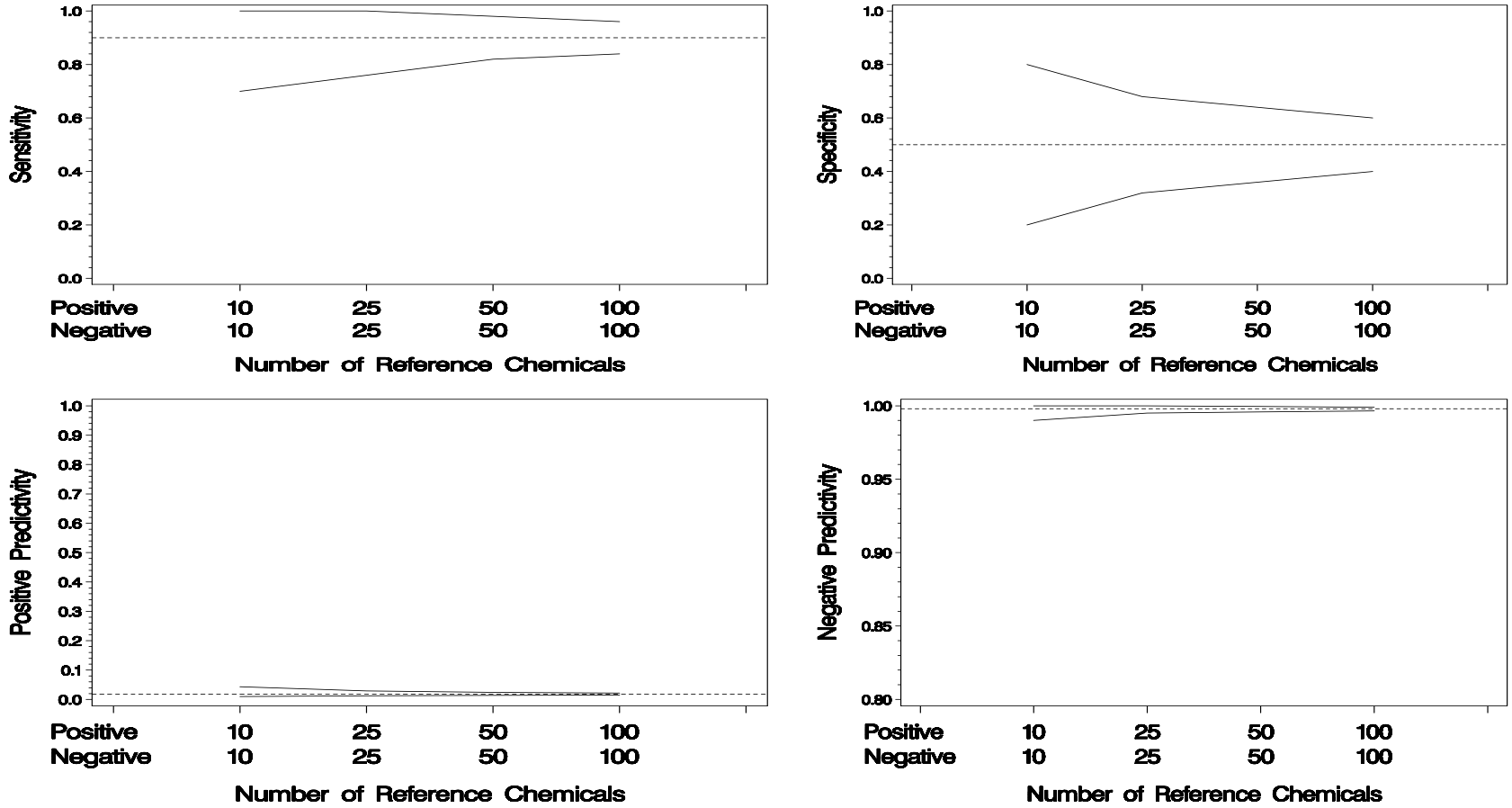


Figure 6-a. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.9, Probability of True Positive Reference=0.01. N1 = N2. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

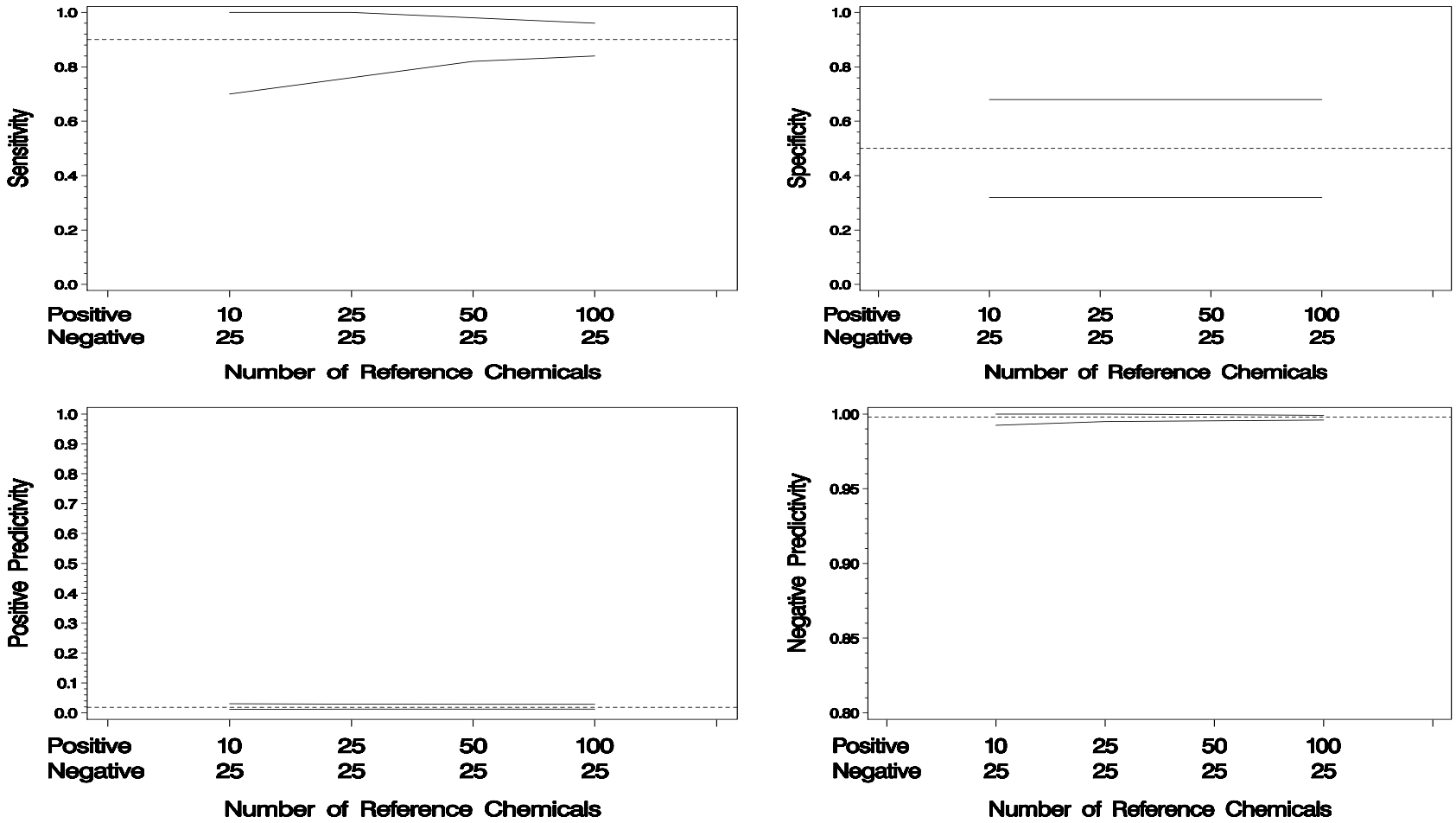


Figure 6-b. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.01. N2 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**

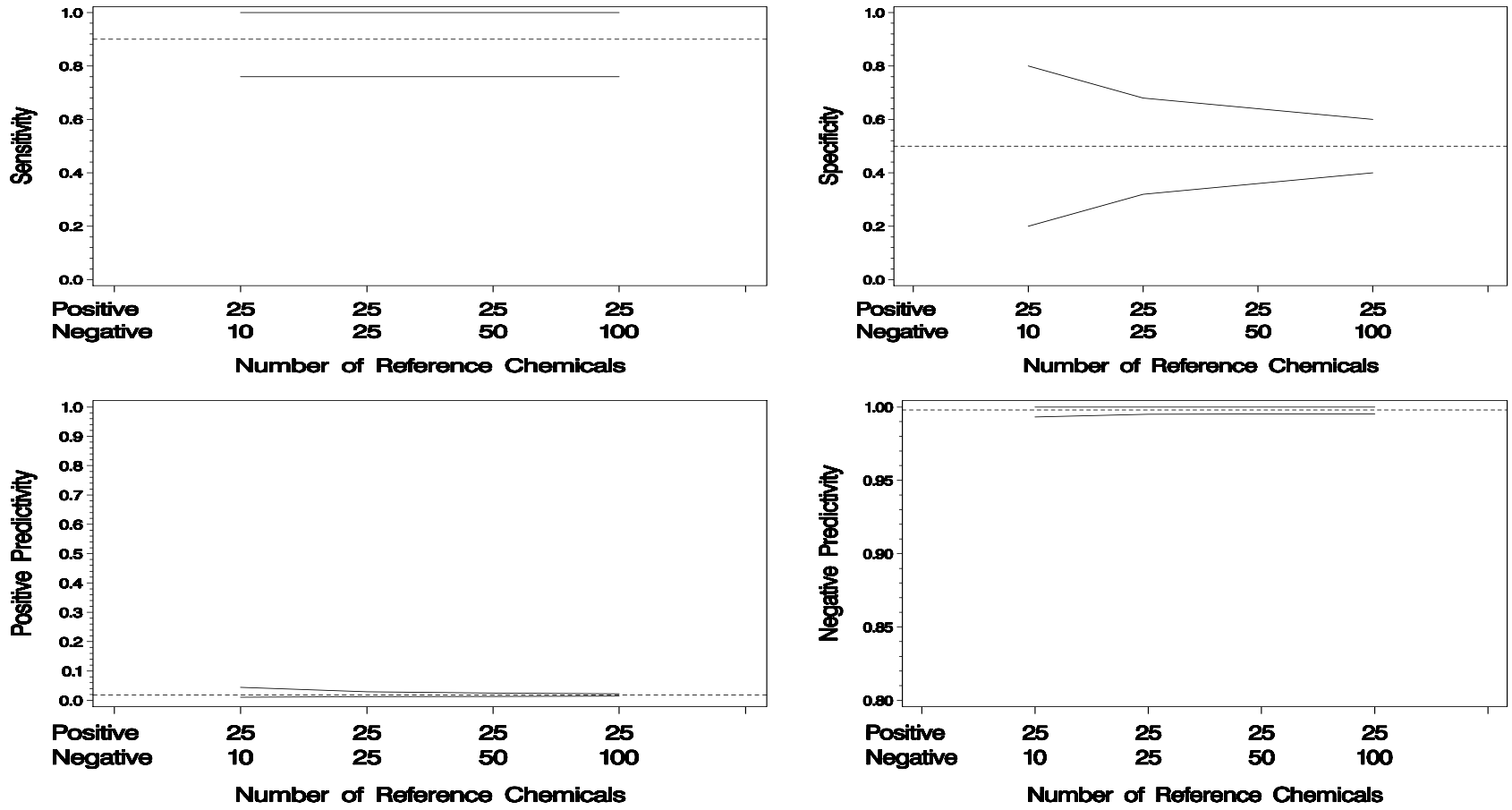


Figure 6-c. **95% Confidence Intervals for Cooper Statistics as a Function of Numbers of Positive and Negative Reference Chemicals. Based on 1,000 Monte Carlo Samples. Sensitivity=0.9, Specificity=0.5, Probability of True Positive Reference=0.01. N1 = 25. (Dotted Reference Lines are the Assumed Cooper Statistics Population Values).**